BLA Clinical Review Memorandum

Application Type	Supplemental Biologics License Application (sBLA)
STN	125106/1469
CBER Received Date	December 20, 2020
PDUFA Goal Date	(Deprioritized)
Division / Office	DVRPA / OVRR
Priority Review (Yes/No)	No
Reviewer Name	Lucia Lee, MD
Review Completion Date / Stamped Date	October 7, 2022
Supervisory Concurrence	Douglas Pratt, MD, MPH Associate Director, Medical Affairs DVRPA, OVRR, CBER
Applicant	GlaxoSmithKline Biologicals
Established Name	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed
Trade Name	Boostrix
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	Each 0.5-mL dose contains 5 Lf of tetanus toxoid, 2.5 Lf of diphtheria toxoid, 8 mcg of inactivated PT, 8 mcg of FHA, and 2.5 mcg of PRN (69 kiloDalton outer membrane protein), 0.3 mg aluminum (as aluminum hydroxide) as adjuvant.
Dosage Form and Route of Administration	Suspension, intramuscular
Dosing Regimen	Single dose during 3rd trimester of pregnancy
New Indication and Intended Population	Immunization during the third trimester of pregnancy to prevent pertussis in infants younger than 2 months of age
Orphan Designated (Yes/No)	No

TABLE OF CONTENTS

GLOSSARY

AE	adverse event
ACIP	Advisory Committee on Immunization Practices
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Review
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CLR	conditional logistic regression
DVRPA	Division of Vaccines and Related Product Applications
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
FDA	US Food and Drug Administration
FHA	filamentous hemagglutinin
GMC	geometric mean concentration
IDMC	Independent Data Monitoring Committee
MAP	meta-analytic prior
NCT	National Clinical Trial
NIBSC	National Institute for Biological Standards and Control
PHE	Public Health England
PREA	Pediatric Research Equity Act
PRN	pertactin
PT	pertussis toxoid
RCS	retrospective cohort study
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SLR	systematic literature review
SRT	Safety Review Team
STN	Submission Tracking Number
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed
US	United States
VE	vaccine effectiveness
WHO	World Health Organization

1. Executive Summary

GlaxoSmithKline (GSK) Biologicals submitted a Biologics License Application supplement (sBLA) to support an indication for Boostrix immunization during the third trimester of pregnancy to prevent pertussis in infants younger than 2 months of age.

The effectiveness of Boostrix immunization during the third trimester of pregnancy to prevent pertussis among infants <2 months of age was based on a re-analysis of Boostrix data (study EPI-PERTUSSIS-052) from an observational case-control study of Tdap vaccine effectiveness (VE) within a Bayesian meta-analysis framework. A conditional logistic regression model controlling for age, maternal education, and family size was fit to data from 108 cases (including 4 cases whose mothers received Boostrix during the third trimester) and 183 controls (including 18 whose mothers received Boostrix during the third trimester) matched by age (<2 weeks old, ≥2 weeks old) and birth hospital. The preliminary VE estimate was 78.0% (95% CI: -38.0, 96.5) for Boostrix vaccination during the third trimester of pregnancy. This preliminary effectiveness estimate was updated using a Bayesian meta-analysis with an informative prior constructed from four observational studies that provided estimates of the VE to prevent pertussis in infants whose mothers were immunized with Boostrix (US or non-US formulation) during pregnancy. When the informative prior had 20% weight, the Bayesian update resulted in a VE of 81.5% (95% credible interval: 12.9, 94.5). When the informative prior had 90% weight, the Bayesian update resulted in a VE of 83.4% (95% credible interval: 55.7, 92.5). The VE point estimates were consistent, regardless of the weight applied to the informative prior, which additionally supported Boostrix effectiveness against pertussis in infants less than 2 months old when administered to their mothers during the third trimester of pregnancy.

The safety of non-US formulation Boostrix administered to women during the third trimester of pregnancy (Boostrix n=341, placebo n=346) was evaluated in study DTPA-Boostrix-047, a randomized, controlled clinical trial. No vaccine-related adverse effects on pregnancy or the fetus/newborn child were identified. The safety data with the non-US formulation are relevant because the non-US formulation of Boostrix contains the same antigens and in the same quantities as Boostrix. The non-US formulation is manufactured to contain 0.5 mg aluminum per dose.

In follow-up studies (DTPA-Boostrix-048 and -049) of infants born to study DTPA-Boostrix-047 maternal participants, reduced pertussis antibody responses to pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN) were observed in these infants following a primary immunization series with non-US formulation Boostrix and to PT and FHA following a booster dose with the same DTaP vaccine, compared to corresponding pertussis responses in infants born to study DTPA-Boostrix-047 mothers who received placebo during pregnancy. Pertussis in infants is a serious medical condition and can be associated with severe complications and long-term sequelae. The benefit of protection from maternal antibodies in infants younger than 2 months of age outweighs the potential risks and uncertainties of diminished pertussis effectiveness later in childhood in DTaP-vaccinated infants born to mothers who received non-US formulation Boostrix during the third trimester of pregnancy.

In conclusion, the safety and effectiveness data in this application support an update to the Boostrix prescribing information for the proposed indication and use.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The number of participants was too small to conduct meaningful effectiveness analyses based on race and ethnicity. In study DTPA-Boostrix-047, the number of participants was too small to conduct meaningful safety analyses based on race, and information about ethnicity for Tdap and comparator groups was not provided.

1.2 Patient Experience Data

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2. Clinical and Regulatory Background

Boostrix was initially approved by FDA in 2005 as a single dose for active booster immunization against tetanus, diphtheria, and pertussis in individuals ages 10 to18 years of age. In 2008, the approved usage was extended to include individuals 18 through 64 years of age, and in 2011 to include individuals 65 years and older. In 2020, the dosage and administration section of the Boostrix prescribing information was again revised to provide for an additional dose 9 years or more after the initial dose of a Tdap vaccine. Please see Boostrix US prescribing information for additional information (FDA 2022).

Most serious pertussis cases, hospitalizations, and deaths occur in infants less than 2 months of age who are too young to benefit from active immunization. Other measures were considered

by public health officials to prevent pertussis in young infants and early recommendations were directed at preventing pertussis by assuring vaccination of close contacts of newborn infants in a strategy termed “cocooning”; this approach met with limited success in controlling pertussis in infants.

In 2011, in an effort to further reduce the increased burden of pertussis in infants observed in previous years, the Advisory Committee on Immunization Practices (ACIP) and the Centers for Disease Control and Prevention (CDC) recommended that unvaccinated pregnant women receive a dose of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) (CDC 2011). In 2012, ACIP made recommendations to extend the use of Tdap vaccines during the third trimester of each pregnancy; the updated recommendation was published in the *Morbidity and Mortality Weekly Report* in 2013, and subsequently implemented.

CDC recommendations for use of Tdap vaccines during pregnancy were not inconsistent with the existing prescribing information for Boostrix as there are no contraindications to use of Boostrix during pregnancy. However, the safety and effectiveness of Boostrix for prevention of pertussis in the infants of individuals vaccinated during pregnancy through passive immunization have not previously been addressed in the prescribing information. With this BLA supplement the Applicant submitted data intended to support the use of Boostrix when administered to pregnant individuals for prevention of pertussis in their infants less than 2 months of age, and revisions to the relevant sections of the prescribing information.

2.1 Disease or Health-Related Condition(s) Studied

Pertussis disease, caused by the bacterium *Bordetella pertussis*, is a highly contagious respiratory illness affecting all age groups. The morbidity associated with pertussis is highest in infants <6 months of age; in 2021, the highest incidence of reported pertussis cases in the US was in infants <6 months of age, with 3.6/per 100,000, of which 31% were hospitalized (CDC 2021a). The case fatality rate for pertussis among infants younger than six months of age was approximately 1%, with the majority of deaths occurring in those younger than two months of age (CDC 2021a).

The most common complications of pertussis infection in infants include apnea, pneumonia, and weight loss secondary to feeding difficulties and post-tussive vomiting. Other complications include seizures and encephalopathy.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Management of infant pertussis infection includes antimicrobial therapy and supportive care. Preventive measures include age-appropriate immunization against pertussis for infants, children, adolescents, adults, and unimmunized/partially immunized close contacts of the index case.

2.3 Safety and Efficacy of Pharmacologically Related Products

Adacel (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed; Sanofi Pasteur Ltd.) is approved by the FDA for active booster immunization against tetanus, diphtheria and pertussis for persons 10 through 64 years of age. Please see the Adacel US prescribing information (FDA 2022).

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Please see section 6.2 of the Boostrix US package insert regarding adverse events identified during postapproval use of Boostrix worldwide. A Boostrix formulation containing the same vaccine antigens and 0.5 mg of aluminum as aluminum hydroxide adjuvant is approved in >45 countries, including countries in Europe.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

September 2014, Type C meeting

The feasibility of conducting a randomized, placebo-controlled Boostrix (US formulation) maternal immunization study in the US was considered challenging due to the existing ACIP recommendation that all pregnant women receive Tdap vaccination during each pregnancy and low incidence of pertussis in young infants. Results from a study conducted in other countries were less generalizable to a US population due to differences in medical standards of care, population characteristics, infant primary and booster pertussis vaccination schedules and differences in vaccine formulations (higher aluminum content (0.5 mg) in adjuvant of non-US formulation). Also, following the initial recommendation by the ACIP in 2011 to vaccinate during pregnancy, multiple countries implemented similar recommendations, including the United Kingdom, Belgium, New Zealand, Israel, Central/South America, certain provinces in Australia and Spain, and Canada.

July 2016-June 2019

A protocol for an epidemiological study to collect safety data about Boostrix administered to pregnant women (study EPI-PERTUSSIS-047 US DB) was submitted for CBER review, and the study started after adequately addressing CBER comments.

The Applicant proposed a re-analysis (study EPI-PERTUSSIS-052 VE DB US) of a dataset from a CDC study (Skoff et al. 2017) designed to evaluate the effectiveness of Tdap regardless of brand, when administered to mothers during pregnancy, to protect against pertussis in infants younger than 2 months of age. In this re-analysis, only effectiveness data relevant to Boostrix were considered. Additional supportive analyses would be performed to characterize Boostrix effectiveness using available data, such as an integrated analysis in a Bayesian framework in which data from the non-US formulation of Boostrix were used to generate a prior.

May 2020, Pre-sBLA Meeting

CBER generally agreed with the Applicant's plan for integrated analysis of study EPI-PERTUSSIS-052 VE DB US effectiveness data in a Bayesian framework and with the studies to be used in the integrated Bayesian analysis to generate a prior. Additional CBER requests for information about the code intended to be used for the analysis were communicated on September 17, 2020; the Applicant's written responses were submitted on October 6, 2020 and considered acceptable by CBER on November 3, 2020. Please see section 5.5.2 for further details.

2.6 Other Relevant Background Information

Safety and effectiveness data with the non-US Boostrix formulation submitted in this sBLA were not intended by the Applicant to support approval of the non-US Boostrix formulation for use in the US.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICE

3.1 Submission Quality and Completeness

The application was acceptable for filing the sBLA. However, multiple information requests were communicated to the Applicant to clarify, verify, and update the dataset used for EPI-PERTUSSIS-052 analyses to support the effectiveness evaluation. See sections 4 and 5.2 for additional details.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Independent audits of 8 clinical sites were conducted, all of which complied with International Conference for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practices guidelines and 21 CFR 601.2. Given the current global COVID-19 public health emergency and the geographic location of the study sites, the CBER Bioresearch Monitoring reviewer recommended a waiver of clinical site inspections and the Review Committee concurred with this recommendation. Following review of the study reports, no deficiencies were identified that would affect the integrity of the clinical data submitted in this sBLA.

3.3 Financial Disclosures

For the CDC case-control study (Skoff et al. 2017), the 11 authors who were also study investigators at the Emerging Infection Program Network sites reported no conflicts of interest or financial relationships relevant to the study. GSK study EPI-PERTUSSIS-052 VE US DB was a re-analysis from the CDC study dataset.

Covered clinical study: The Applicant provided financial disclosures for study investigators participating in studies DTPA-047, DTPA-048, and DTPA-049.
Was a list of clinical investigators provided? ☒ Yes ☐ No (Request list from applicant)
Total number of investigators identified: 203
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____

Significant payments of other sorts: _____

Proprietary interest in the product tested held by investigator: _____

Significant equity interest held by investigator in sponsor of covered study: _____

Is an attachment provided with details of the disclosable financial interests/arrangements? ☐ Yes ☐ No (Request details from applicant)

Is a description of the steps taken to minimize potential bias provided? ☐ Yes ☐ No (Request information from applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0

Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant)

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

No substantive issues were identified by the CBER CMC reviewer that would affect interpretation of the clinical data submitted in this sBLA.

4.2 Assay Validation

The serological assays used to assess responses to the diphtheria (D), tetanus (T), and acellular pertussis (aP) antigens were redeveloped in 2014. The pertussis enzyme-linked immunosorbent assay (ELISA) was calibrated against the (b) (4) for PT, FHA and PRN antigens; antibody concentrations are now reported in IU/m instead of ELISA units per milliliter (ELU/mL). The Tdap ELISA assay cutoffs used for analyses in this sBLA were (b) (4) IU/mL for anti-D, (b) (4) IU/mL for anti-T, 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA and 2.187 IU/mL for anti-PRN. Following review of the assay validation information, the CBER assay reviewer concluded that the D, T, and aP serological assays supported their intended use.

4.3 Nonclinical Pharmacology/Toxicology

This submission contained no new or updated pre-clinical information.

4.5 Statistical

The statistical reviewer was able to satisfactorily verify the data submitted to the sBLA. Based on EPI-PERTUSSIS-052 Bayesian analyses and sensitivity analyses performed by the Applicant and FDA, the statistical reviewer concluded that overall the results suggested Boostrix was statistically likely to be effective for the intended indication, and the results were robust to the analysis methods and missing data. The EPI-PERTUSSIS-052 analyses had some

limitations, since the re-analyses were performed *post hoc* and based on data from a retrospective study (Skoff et al. 2017), and limited study power. Please see CBER statistical (Dr. Jennifer Kirk) review memo for further details about the statistical methods.

Study EPI-PERTUSSIS-052 Bayesian Analysis Prior: The robustness of the 4 observational studies conducted outside the US with the non-US formulation of Boostrix informed the Bayesian analysis prior was assessed. supported the effectiveness of Boostrix immunization of individuals in the third trimester of pregnancy to prevent pertussis among infants < 3 months old, with an estimated VE of approximately 90% (except for Saul et al., 2018 who found a VE of 69%, due in part to sensitive case ascertainment for mild disease). Please see CBER epidemiology (Dr. Diane Gubernot) review memo for additional information and section 5.5.2.

4.6 Pharmacovigilance

Although the safety data submitted from clinical trial DTPA-Boostrix-047 (Boostrix n=341, placebo n=346) and pregnancy registry (EPI-PERTUSSIS-028) did not identify risks to the mother, the fetus, or the infant from routine vaccination in the third trimester of pregnancy, interpretation of potential risks associated with vaccination during pregnancy was limited because a significant percentage of pregnancy registry participants were lost to follow-up (82%; 1246 of 1523 participants). Please see CBER pharmacovigilance (Dr. Jonathan Reich) review memo for additional information. To address FDA's concern about a potentially incomplete safety profile of Boostrix vaccination during pregnancy, the Applicant committed to conduct a new pregnancy registry as a postmarketing study (EPI-PERTUSSIS-075 VS US PR). See section 11.6 for additional details. The Applicant will assess the feasibility of partnering with an organization that has well-established measures proved efficient to retain participants and to provide more complete data.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This sBLA contains results from study EPI-PERTUSSIS-052 VE US DB, a re-analysis of a CDC case-control study, and reports from studies DTPA-BOOSTRIX-047, -048 PRI, and -049 BST. EPI-PERTUSSIS-052 VE US DB was the main study intended to support effectiveness of Boostrix when administered during the 3rd trimester of pregnancy. Study DTPA-BOOSTRIX-047 supported the safety of Boostrix administered to women during pregnancy, and neonatal outcomes, and immunogenicity data from studies DTPA-BOOSTRIX-048 PRI and -049 BST provided assessments of D, T and pertussis antibody responses following primary immunization and booster dose with a DTaP-containing vaccine, in infants born to Boostrix-vaccinated mothers.

5.2 BLA Documents That Serve as the Basis for the Clinical Review

The following amendments were reviewed in support of this application:
Amendment 0

- Module 1, all sections: Administrative information and prescribing information
- Module 2, sections 2.2 introduction, 2.5 clinical overview, 2.7 summaries of clinical efficacy and safety, synopses of individual studies
- Module 5, sections 5.2 tabular listing of all clinical studies, section 5.3 clinical study reports

Responses to CBER information requests:

- Amendment 1- initial pediatric study plan

- Amendment 2- request for partial waiver for Pediatric Research Equity Act (PREA) studies, investigator's brochure
- Amendment 3- clinical sites for studies DTPA-047, -048 PRI, and 049 BST
- Amendment 4- study EPI-PERTUSSIS-052- clarify vaccine brand and maternal exposure timing, provide additional data to derive analysis variables
- Amendment 5- study EPI-PERTUSSIS-052- updated response for amendment 4
- Amendment 6- study EPI-PERTUSSIS-052- further clarify maternal exposure
- Amendment 7- study EPI-PERTUSSIS-052- sensitivity analyses, further clarify records with unknown vaccine brand
- Amendment 8- pregnancy literature review
- Amendment 10- study EPI-PERTUSSIS-052- updated dataset
- Amendment 12- Bayesian analyses of VE based on updated dataset
- Amendment 14- clarified studies described in section 8.1 of package insert
- Amendment 15- studies DTPA-Boostrix-048 and DTPA-Boostrix-049: subgroup analyses
- Amendment 16- package insert: Applicant responses to CBER comments
- Amendment 17- revised package insert
- Amendment 19- revised package insert, summary table to support pregnancy registry results described in section 8.1
- Amendment 20- revised package insert

5.3 Table of Studies/Clinical Trials

Study ID #/ Location/ NCT #	Description and Pertinent Study Objectives	Boostrix[a] N	Comparator[a,b] N
Main study			
EPI-PERTUSSIS-052 VE US DB/ USA/ NCT03973905	Re-analysis of data collected from a case-control study. EPI-PERTUSSIS-052 primary objective: to assess effectiveness of Boostrix immunization during 3rd trimester of pregnancy to prevent pertussis in infants <2 months of age	Infants: 108	Infants: 183
Supportive studies			
DTPA-BOOSTRIX-047/ Australia, Canada, Europe/ NCT02377349	Phase 4, observer-blind, randomized, placebo-controlled; to demonstrate the presence of maternal antibodies against pertussis in cord blood, and to evaluate safety of Boostrix (non-US formulation) administered to pregnant women 18-45 years of age	Women: 341	Women: 346
DTPA-BOOSTRIX-048 PRI/ Australia, Canada, Europe/ NCT02422264	Follow-up open-label study in infants born to mothers enrolled in study DTPA-047; to assess pertussis antibody responses after a DTaP-HBV-IPV-Hib primary series	Infants: 268	Infants: 274
DTPA-BOOSTRIX-049 BST/ Australia, Canada, Europe/ NCT02853929	Follow-up open-label study in toddlers 11-18 months of age who completed DTaP-HBV-IPV-Hib primary series in study DTPA-048; to assess pertussis antibody responses after a DTaP-HBV-IPV-Hib booster dose	Toddlers: 229	Toddlers: 250

Source: adapted from m5-2-tab-listing-of-all-clin-studies-dtpa.pdf, pages 1-4.

a. Total vaccinated cohort: study DTPA-047.
b. According-to-protocol immunogenicity cohort: studies DTPA-048 and -049.

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

There were no issues or concerns identified in this sBLA that would have benefitted from a vaccines advisory committee discussion.

5.4.2 External Consults/Collaborations

Not applicable

5.5 Literature Reviewed

5.5.1 References

Andersen AR, Kolmos SK, Flanagan KL, Benn CS (2022). Systematic review and meta-analysis of the effect of pertussis vaccine in pregnancy on the risk of chorioamnionitis, non-pertussis infectious diseases and other adverse pregnancy outcomes. *Vaccine*. 2022;40(11):1572-1582.

Andrews A, Campbell H, Ribeiro S, Fry N, Amirthalingham G (2020). Boostrix-IPV Report: Effectiveness of Maternal Pertussis Vaccination in Prevention of Confirmed Pertussis in Children in England Using the Screening Method Report to 30 September 2018. Public Health England. Unpublished. 2020.

Amirthalingam G, Campbell H, Ribeiro S, et al. Sustained Effectiveness of the Maternal Pertussis Immunization Program in England 3 Years Following Introduction. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2016;63(suppl 4):S236-s43.

Bellido-Blasco J, Guiral-Rodrigo S, Míguez-Santiyán A, Salazar-Cifre A, GonzálezMorán F. A case-control study to assess the effectiveness of pertussis vaccination during pregnancy on newborns, Valencian community, Spain, 1 March 2015 to 29 February 2016. *Euro Surveill*. 2017;22 (22).

Centers for Disease Control and Prevention (CDC) (2011). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) in pregnant women and persons who have or anticipate having close contact with an infant aged <12 months --- Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR. Morbidity and mortality weekly report*, *60*(41), 1424–1426. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6041a4.htm. Accessed September 19, 2022.

Centers for Disease Control and Prevention (CDC) (2021a). 2021 Provisional pertussis surveillance report. https://www.cdc.gov/pertussis/downloads/pertuss-surv-report-2021_provisional.pdf. Accessed September 19, 2022.

Centers for Disease Control and Prevention (CDC) (2021b). Metropolitan Atlanta Congenital Defects Program. https://www.cdc.gov/ncbddd/birthdefects/macdp.html. Accessed September 19, 2022.

European Medicines Agency (EMA) (2006). Guideline on the exposure to medicinal products during pregnancy: need for postauthorization data (2006). https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-exposure-medicinal-products-during-pregnancy-need-post-authorisation-data_en.pdf. Accessed September 19, 2022.

Saul N, Wang K, Bag S, Baldwin H, Alexander K, Chandra M, et al. Effectiveness of maternal pertussis vaccination in preventing infection and disease in infants: The NSW Public Health Network case-control study. *Vaccine*. 2018;36(14):1887-1892.

Schmidli, H., Gsteiger, S., Roychoudhury, S., et al. (2014). Robust meta-analytic-predictive priors in clinical trials with historical control information. *Biometrics*, *70*(4), 1023–1032. https://doi.org/10.1111/biom.12242. Accessed September 19, 2022.

Skoff, TH, Blain, AE, Watt, J. et al. (2017). Impact of the US Maternal Tetanus, Diphtheria, and Acellular Pertussis Vaccination Program on Preventing Pertussis in Infants <2 Months of Age: A Case-control Evaluation. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, *65*(12), 1977–1983. https://doi.org/10.1093/cid/cix724. Accessed September 19, 2022.

Uriarte PS, Rodríguez SSJ, Sancristobal IG, Agirre NM. Effectiveness of dTpa vaccination during pregnancy in preventing whooping cough in infants under 3 months of age. Bizkaia, Basque Country, Spain. *Heliyon*. 2019; 5 (2): e01207.

US Food and Drug Administration (FDA) (2022). Vaccines licensed for use in the United States. https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states. Accessed September 19, 2022.

Vygen-Bonnet S, Hellenbrand W, Garbe E, von Kries R, Bogdan C, Heininger U, Röbl-Mathieu M, Harder T (2020). Safety and effectiveness of acellular pertussis vaccination during pregnancy: a systematic review. *BMC Infect Dis.* 2020;20(1):136.

5.5.2 Review of Studies to Inform the Bayesian Analysis Prior, Study EPI-PERTUSSIS-052

The EPI-PERTUSSIS-052 statistical analysis plan contains tables 1-3, figure 1, and literature references cited in this section. One of the studies, Amirthalingam et al. (2016), was replaced by an unpublished report from Public Health England (PHE) (Andrews et al. 2020) that uses the same analysis methods as Amirthalingam et al. but comprises a longer period of follow-up.

To evaluate the effectiveness of Boostrix maternal immunization against pertussis disease in infants (study EPI-PERTUSSIS-052 VE DB US) GSK established a data use agreement with the CDC to access the dataset of a large CDC-sponsored study (Skoff et al. 2017). In this CDC-sponsored collaborative study, network sites evaluated the effectiveness of Tdap vaccination (Adacel or Boostrix) during pregnancy for preventing pertussis in infants <2 months of age (Skoff et al. 2017). However, after exclusion of controls matched to cases born to mothers vaccinated with Adacel, or vaccinated with Tdap but without vaccine brand specification, cases with no matched controls and controls not matched to any remaining case, the study population was

reduced to 108 cases and 183 matched controls, which provided insufficient power to confirm the effectiveness of Boostrix maternal vaccination when administered during third trimester of pregnancy. Adjusting for infant's age, maternal education and household size, the effectiveness of Boostrix maternal vaccination when administered during third trimester of pregnancy was 78.0% (95% CI: -38.0, 96.5). While the point estimate was consistent with the non-brand specific analysis provided in the Skoff et al. study, the effectiveness of Boostrix maternal immunization was not confirmed by this study alone, as indicated by the wide 95% confidence interval and lower bound less than 0.

Thus, CBER requested the Applicant to perform additional supportive analyses to characterize Boostrix effectiveness leveraging non-US formulation data in a Bayesian framework. In this framework, the selected observational studies (Table 2) were used to define a prior for a Bayesian reanalysis of the Skoff et al. data.

Based on FDA's request, the Applicant performed a systematic literature review to identify epidemiological observational studies published in peer-reviewed journals that evaluated the effectiveness of maternal immunization with Boostrix or Boostrix-Polio at preventing pertussis disease in young infants (under 2-3 months of age) who had not yet received their first dose in the infant immunization series. Out of 13 studies on the effectiveness of maternal immunization with Tdap vaccine identified by the Applicant, 4 provided estimates of the effectiveness of Boostrix or Boostrix-Polio (Table 3). The use of Boostrix or Boostrix Polio is explicitly mentioned in three of the publications (Amirthalingam et al. 2016; Saul et al. 2018; Uriarte et al. 2019). Although one publication from Spain (Bellido-Blasco et al. 2017) did not mention the vaccine brand, the study investigator confirmed in a communication with GSK that the vaccine used was Boostrix. In addition to these published studies, GSK entered into an agreement with PHE for the provision of a report of an analysis performed by PHE on the effectiveness of maternal immunization with Boostrix-Polio (at the time this sBLA was submitted to FDA, this analysis had not been published in peer-reviewed journals). The study report prepared by PHE at the Applicant's request used the screening method to measure VE, as in the study published by Amirthalingam et al. (2016) and used the same data sources, but covered a longer period of time (i.e., 4 years).

The VE estimates used by the Applicant from these studies to define a prior for a Bayesian analysis were in line with the objective of only using estimates of VE for pertussis cases occurring before 3 months of age and when most infants had not yet started DTP infant immunization. Moreover, in cases in which the paper provided multiple VE estimates, GSK selected the most conservative VE estimate (i.e., the estimate with the lowest point estimate of VE). Also, the studies with the highest quality were also the largest and, therefore, contributed the most weight towards the prior (Figure 1).

Based on the available information, including the justification for the selection of the studies and the study quality evaluations provided by the Applicant, CBER considers that the procedures used by the Applicant to select the papers, and to select the VE estimates to be used to define the prior for the Bayesian analysis were appropriate.

5.5.3 Systematic Literature Review Addressing Safety of Boostrix Administered during Pregnancy and Neonatal Outcomes

To comprehensively address the safety of Boostrix use in pregnant women, CBER, on April 14, 2022, asked the Applicant to provide a systematic literature review (SLR) on pregnancy and neonatal outcomes associated with use of US and non-US formulations of Boostrix both inside

and outside the US. In their response, GSK presented data on the safety of maternal immunization with Boostrix based on an SLR of the safety of Tdap immunization during pregnancy published by Vygen-Bonnet et al. in 2020, complemented by the findings from a subsequent SLR and meta-analysis of the effect of pertussis vaccine in pregnancy on the risk of chorioamnionitis, non-pertussis infectious diseases and other adverse pregnancy outcomes (Andersen et al 2022), and by the findings from GSK-sponsored and supported clinical trials and observational studies evaluating the safety of Boostrix use in pregnant women, for which results became available after the conduct of the SLR of Vygen-Bonnet et al. In this review, the Applicant included a total of 16 studies, of which six specifically identified Boostrix. One of them was a randomized trial of Boostrix. All others were observational studies (see Table 1).

The following outcomes were included in the Applicant's review: maternal fever, pre-eclampsia and eclampsia, chorioamnionitis, stillbirth, neonatal death, pre-term birth, low birth weight/small for gestational age and poor fetal growth/intrauterine growth restriction, neonatal sepsis, admission to newborn intensive care unit, and congenital anomalies/malformations.

Eclampsia/preeclampsia risk was evaluated in a randomized trial of Boostrix (which included 341 Boostrix vaccinees and 346 controls) and eight observational studies. In five studies, the sole vaccine was Boostrix. In one observational study (EPI-PERTUSSIS-047 VS DB US), the adjusted relative risk for pre-eclampsia/eclampsia was elevated (RR 1.38 (98.75% CI: 1.21-1.58)). However, this increase was likely due to changes in the background incidence of eclampsia/eclampsia during the two time periods being compared resulting from improved screening, detection, and treatment. In eight studies, which also included the (relatively small) Applicant's randomized, controlled trial of Boostrix (study DTPA-Boostrix-047), there was either a slightly decreased risk of this outcome in vaccinated women or no association. Chorioamnionitis was reported in study DTPA-Boostrix-047and in eight non-randomized studies among which three were Boostrix-specific. In study DTPA-Boostrix-047, no association was found, although the study was of limited size (Boostrix n=341, placebo n=346). Only one of the observational studies (which used the same database as EPI-PERTUSSIS-047) found an association (with intrauterine infection). However, as with EPI-PERTUSSIS-047, the increase was consistent with the background increasing trend of this diagnosis between the two periods being compared.

Congenital anomalies were reported in nine studies. However, in study DTPA-Boostrix-047 and follow-up studies (DTPA-Boostrix-048 and DTPA-Boostrix 049), there was no signal for congenital anomalies. Moreover, CDC recommends that pertussis vaccination should be preferentially administered during the 27th through 36th week of each pregnancy, too late for an association with congenital anomalies to be of concern. There were no signals of concern with any of the other outcomes evaluated.

In summary, this systematic and comprehensive review included safety data from 16 studies, including one randomized controlled trial and 15 observational studies, based on data from over 2.5 million pregnancies. No conclusive association of any adverse outcome with Boostrix vaccination during pregnancy was found for the mother or infant. However, these (overall reassuring) findings also do not demonstrate conclusively that Boostrix vaccination is not causally associated with adverse events of pregnancy due to small numbers of participants in the randomized trial and inherent limitations of observational study designs.

In conclusion, the results of this comprehensive literature review are consistent with the Applicant's statement that the evidence currently available supports the safety for both the women vaccinated with Boostrix during their pregnancy and their infants.

Table 1. Characteristics of Studies Assessing the Safety of Tdap Maternal Immunization (Studies Including Boostrix and Unspecified Vaccine Brands)

Authors and Country	Setting/Data Sources	Study Design/ Period	Inclusion (I) and Exclusion (E) Criteria	Intervention/ Comparison	Final N/ N Potentially Eligible/ (%)	N Intervention Group	N Control Group	Outcomes
Berenson *et al.*, 2016; USA	University hospital	RCS, 2012–2014	I: Singleton pregnancies delivered ≥27 WG; E: Women with < 4 clinic visits during pregnancy	Tdap (vaccine not specified) during pregnancy vs. no Tdap	–	1109	650	obstetric and perinatal complications
DeSilva *et al.*, 2016; USA	7 Vaccine Safety Datalink sites (Analysis of health insurance-based electronic health records)	RCS, 2007–2013	I: Singleton live births, women continuously insured from 6 months before LMP through 6 weeks postpartum, with ≥1 outpatient visit(s) during pregnancy. I Infants: birth weight and gestational age available; enrolled in health insurance for ≥4 months in first YoL, with ≥1 outpatient visit(s); E: Infants with exposures increasing risk for structural birth defects (maternal diabetes or use of teratogenic medications, congenital infections, and chromosomal abnormalities)	Tdap (vaccine not specified) during pregnancy vs. no Tdap	324,463 singleton live births	41,654	282,809	microcephaly and other selected major structural birth defects
DeSilva *et al.*, 2017; USA	7 Vaccine Safety Datalink sites (Analysis of health insurance-based electronic health records)	RCS, 2010-2013	I: Singleton live births, women continuously insured from 6 months before LMP through 6 weeks postpartum, with ≥1 outpatient visit(s) during pregnancy. I Infants: birth weight and gestational age available; enrolled in health insurance for ≥4 months in first YoL, with ≥1 outpatient visit(s); E: Women who received live virus vaccines during pregnancy	Tdap mostly at 27–36 WG (vaccine not specified) vs. no Tdap	197,654 /243,981 (81%) live births	45,008	152,556	obstetric and perinatal complications

Authors and Country	Setting/Data Sources	Study Design/ Period	Inclusion (I) and Exclusion (E) Criteria	Intervention/ Comparison	Final N/ N Potentially Eligible/ (%)	N Intervention Group	N Control Group	Outcomes
Fakhraei *et al.,* 2021; Canada	Population-based cohort study	RCS, 2012-2017	I: eligible live births and stillbirths > 20 weeks E: not Ontario resident, maternal age <12 or >50 years at delivery; live birth with implausible birth weight and gestational age combinations	Tdap (vaccine not specified) < 20 wk, 20- 26 w, 27-32 wk (recommended timing) and >32 weeks	615,213 live births and stillbirths	11,519	603,694	perinatal outcomes
Griffin *et al*., 2018; New Zealand	Nationwide linked administrative health databases	RCS, 2013	I: All pregnant women who reached 28–38 WG in 2013; E Women: pregnancies < 20 WG or missing maternal or gestational age; E Infants: live born babies < 28 WG or BW < 400 g	Tdap (Boostrix) at 28– 38 WG vs. no Tdap	68,550/ 73,817 (93%)	8178	60,372	obstetric, perinatal and neonatal outcomes
Hall *et al*., 2020 ; USA	Department of Defense Birth and Infant Health Research program, which identifies pregnancies, live births, and associated health outcomes among TRICARE beneficiaries (i.e., those enrolled in the Military Health System)	RCS, 2006-1014	I: military women who were on active duty status for the duration of their pregnancy. E: Pregnancies for which outcomes could not be ascertained were excluded from analyses ("unknown outcomes"), as were ectopic and molar pregnancies, pregnancies ending in elective abortions, pregnancies in which women received more than one Tdap vaccine, and multiple gestations.	Tdap (vaccine not specified) with either inadvertent exposure (receipt between 0 and 13 WG, i.e., the first trimester) or recommended exposure (receipt of the Tdap vaccine between 27 and 36 WG) vs no Tdap during pregnancy	145,883 pregnancies identified among active duty women	1272 (0.9%) exposed during the first trimester 9438 (6.5%) during 27–36 WG	131,450	pregnancy and infant outcomes

Authors and Country	Setting/Data Sources	Study Design/ Period	Inclusion (I) and Exclusion (E) Criteria	Intervention/ Comparison	Final N/ N Potentially Eligible/ (%)	N Intervention Group	N Control Group	Outcomes
Kharbanda *et al*., 2016; USA	Vaccine Safety Datalink sites (Analysis of health insurance-based electronic health records)	RCS, 2007–2013	I: Women 14–49 years of age at delivery with singleton pregnancies ending in live birth, continuously insured from 6 months before LMP through 6 weeks postpartum, ≥1 outpatient visit at an affiliated site and with birth weight and gestational age recorded; E: Women who received live virus vaccines during pregnancy or who received Tdap in the 7 days after the estimated pregnancy start date or in the 7 days before delivery; incomplete birth data	Tdap (vaccine not specified) during pregnancy vs. no Tdap	427,097/ 631,256 (68%)	53,885	109,253	acute safety endpoints in 0–42 days after vaccination
Layton *et al*., 2017; USA	MarketScan Commercial Claims and Encounters (Truven Health Analytics) claims databases of employer-based commercial health care insurance	RCS, 2010–2014	I: Women with livebirth or stillbirth deliveries; only first observed pregnancy per women; E: Women who delivered at ≤26 WG; women ≤18 years in 13 states with universal childhood immunization policies	Tdap (vaccine not specified) at ≥27 WG; Tdap <27 WG vs. no Tdap	NR	≥27 WG: 123,780 < 27 WG: 25,037	871,177	acute safety endpoints in 0–42 days after vaccination; obstetrical and perinatal complications
Maertens *et al*., 2016; Belgium	5 hospitals in Antwerp, Belgium	PCS, 2012–2014	I: Women 18–40 years of age with low risk for complications. E: Same as Hoang *et al*.	Tdap (Boostrix) at 22– 33 WG vs. no Tdap	NR	57	42	acute safety outcomes obstetric and perinatal complications

Authors and Country	Setting/Data Sources	Study Design/ Period	Inclusion (I) and Exclusion (E) Criteria	Intervention/ Comparison	Final N/ N Potentially Eligible/ (%)	N Intervention Group	N Control Group	Outcomes
Mohammed *et al*., 2021, Australia	2 obstetric hospitals in South Australia	PCS, 2015-2018	I: Nulliparous women with a singleton pregnancy attending their first antenatal clinic between GA 9 and 16. E: Considered at high risk of pregnancy complications at screening (i.e., experienced three or more previous miscarriages or with pre-existing hypertension or diabetes).	Tdap (not specified) vs. No Tdap during Pregnancy	Tdap any time during pregnancy, 78% within GA 28–32 vs no Tdap during pregnancy	1,019	253	Obstetric and neonatal outcomes
Morgan *et al*., 2015; USA	Parkland clinic-based pre-natal and obstetrical care centers in Dallas County with centralized electronic medical charting system	RCS, 2013–2014	I: All women who delivered at Parkland	Tdap (vaccine not specified) at ≥32 WG vs. no Tdap	NR	7152	226	obstetric and neonatal outcomes
Perrett *et al*., 2020a; Australia, Canada, Czech Republic, Finland, Italy, Spain	Multi-center study; 34 hospital centers	RCT (randomized placebo-controlled, crossover trial); 2015-2017	I: healthy women 18–45 years old, at $27^{0/7}$–$36^{6/7}$weeks' gestation (as established by ultrasound examination), not at known risk of pregnancy-related complications and normal singleton pregnancy. E: Detailed inclusion and exclusion criteria are provided in the Supplementary methods.	Tdap (Boostrix) at $27^{0/7}$–$36^{6/7}$ WG vs. Placebo	TVC 687/ Enrolled 725 (95%)	341	346	pregnancy outcomes and pregnancy-/neonate-related AEs of interest until study end (2 months after delivery)
Petousis-Harris *et al*., 2019; New Zealand	Nationwide linked administrative health databases	RCS, 2013	I: Infants: all- live infants weighing at least 400 g at delivery and born to women who reached 28–38 WG in 2013	Tdap (Boostrix) at 28– 38 WG vs. no Tdap	68,550/ 73,817 (93%)	8,299	61,090	perinatal and neonatal outcomes

Authors and Country	Setting/Data Sources	Study Design/ Period	Inclusion (I) and Exclusion (E) Criteria	Intervention/ Comparison	Final N/ N Potentially Eligible/ (%)	N Intervention Group	N Control Group	Outcomes
Sancovski *et al.*, 2019 ; Brazil (EPI-PERTUSSIS-037 VS BR)	One center in São Bernardo do Campo, São Paulo, Brazil	RCS, 2012-2017	I: women between 18 and 45 y of age at the time of pregnancy, who delivered in the study center, were residents of the city of São Bernardo do Campo, were compliant with the routine antenatal care, and had complete and relevant medical records available. E: transferred to other specialized centers where the medical records would be inaccessible for the study	Tdap (Refortrix, the brand name of Boostrix in Brazil) between 27 and 36 completed WG vs. no Tdap	2,477	1,203	1,259	obstetric and neonatal outcomes, including congenital anomalies in neonates
Shakib *et al*., 2013; USA	Intermountain Healthcare database, Utah	RCS, 2005–2009	I: Pregnant women 12–45 years of age and their babies; E: Women whose pregnancy start date could not be determined; women who had documentation of Tdap vaccine within 3 days prior to delivery	Tdap (vaccine not specified) at any time during pregnancy vs. no Tdap	162,448	138	552	obstetric and perinatal complications; congenital anomalies, complex chronic conditions in 1st YoL
EPI-PERTUSSIS-047 VS DB US – manuscripts under peer-review	Kaiser Permanente Southern California, seven medical center areas	RCS, 2012-2019	I: pregnant women with evidence of prenatal care and continuous membership (allowing up to a 31-day gap) at KPSC between the 1st day of the 27th week of gestation and the index (vaccination) date, E: -	Boostrix vs. no Tdap	33,212	16,606	16,606	obstetric and neonatal outcomes, including congenital anomalies in the first 6 months of life

Source: 125106.1469 amendment 8, pages 6-11, Table 1.
LMP: Last Menstrual Period; RCS retrospective cohort study; RCT: Randomized Controlled Trial; WG weeks of gestation; PCS prospective cohort study; YoL year of life.

6. INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 EPI-PERTUSSIS-052 VE US DB

NCT#03973905
Title: Effectiveness of maternal immunization with Boostrix at preventing pertussis among infants <2 months old in the United States (US): analysis of a dataset from a case-control study conducted in the US by the Centers for Disease Control and Prevention (CDC).

The CDC study was designed as an observational, retrospective, matched, case-control study to evaluate the effectiveness of Tdap regardless of brand, when administered to mothers during pregnancy, to protect against pertussis in infants <2 months of age (Skoff et al. 2017). The VE of Boostrix was assessed in study EPI-PERTUSSIS-052 VE US DB, a re-analysis of the CDC study.

6.1.1 Primary Objective and Endpoint

In study EPI-PERTUSSIS-052, the primary objective was to assess the effectiveness of Boostrix to prevent pertussis in infants younger than 2 months of age, when Boostrix was administered to mothers during the third trimester of pregnancy.*
Primary endpoint: Occurrence of pertussis among infants <2 months old born to women vaccinated with Boostrix during the third trimester of pregnancy.

* Please see section 6.1.2 for definition of vaccination during the third trimester of pregnancy.

6.1.2 Data Sources

CDC study (Skoff et al. 2017)
Pertussis cases and controls were identified from data collected at six sites comprising the CDC's Emerging Infection Program Network; study period for the CDC study was from January 1, 2011, to December 31, 2014.

- Infants
  - Were eligible for enrollment if they were at least 2 days old, born in a hospital in their state of residence, at least 37 weeks of gestational age at birth, not adopted or in foster care, and did not live in a residential care facility.

  - A pertussis case was defined as a cough illness and at least one of the following: laboratory confirmation (PCR or culture), epidemiological linkage to a laboratory-confirmed pertussis case, or cough lasting two or more weeks with paroxysms, inspiratory whoop, or post-tussive vomiting.

    Infants were included as cases if they met the infant eligibility criteria, were living in the catchment area on their cough onset date, and met the pertussis case definition.

  - Potential control infants were identified based on birth certificates of infants born at the same hospital as the corresponding case infant, and with the goal of collecting three controls per case. Infants were eligible as controls if they met the infant eligibility criteria, were born at the same hospital as a case infant, were less than two months old on a case infant's cough onset date, and did not have a pertussis diagnosis prior to the case infant's cough onset date.

- Information about household size, maternal education, household member with a pertussis diagnosis, and infant's age in weeks were obtained from maternal telephone interviews, medical provider interviews, birth certificate records, and surveillance case report forms.

- Maternal Tdap exposure: immunization information, including immunization date and vaccine type, manufacturer, brand, and lot, was collected from medical providers or state immunization registries for the mothers of all enrolled infants.
  - Mothers were categorized as unvaccinated if they had no evidence of at least one Tdap vaccination given at least two weeks prior to their corresponding case infant's cough onset date. If multiple Tdap doses were identified, the most recent was used to classify the mother's exposure relative to pregnancy.

  - Mothers were classified as vaccinated
    - before pregnancy if their most recent Tdap dose was given on or before their pregnancy start date

    - during the 1st or 2nd trimester if their most recent Tdap dose was given after their pregnancy start date and <189 days after their pregnancy start date

    - during the 3rd trimester if their most recent Tdap dose was given at least 189 days after their pregnancy start date and at least 14 days before their infant's date of birth

    - after pregnancy if their most recent Tdap dose was given post-partum or no more than 14 days before their infant's date of birth and at least 14 days before their corresponding case infant's cough onset date.

  - Pregnancy start date was calculated from the infant's date of birth and gestational age.

Please see CBER statistical review memo for comments about the data source limitations (e.g., data collection, case definition, selection of control group, and maternal vaccine exposure definitions).

6.1.3 Statistical Analysis Plan

EPI-PERTUSSIS re-analysis dataset
The analysis of the EPI-PERTUSSIS-052 primary objective was based on a dataset that included all infants born to mothers who were classified as unexposed or as exposed to Boostrix and whose matching stratum included at least one case and one control.

Analyses
Number and percentages of infant pertussis cases and controls of mothers for whom Boostrix administration was recorded before pregnancy, during pregnancy (first, second and third trimester), after pregnancy or who were unexposed to any Tdap vaccine.

VE to support the intended indication took into account both the Boostrix-specific results from Skoff et al. 2017 and Bayesian analyses.

Primary Objective: Frequentist analysis
VE was estimated as (1 – OR) × 100%, where OR is the odds ratio for maternal Boostrix exposure given infant pertussis case status. The OR was estimated using an adjusted conditional logistic regression (CLR) model with a categorial exposure variable: unvaccinated,

vaccinated before pregnancy, vaccinated in the first or second trimester, vaccinated in the third trimester, and vaccinated after pregnancy. Covariates for the adjusted CLR model were selected for the adjusted CLR model if their p-value from a univariate CLR model of the odds of binary exposure (vaccinated or unvaccinated) was less than 0.2. The VE estimate and 95% confidence interval, derived from the asymptotic normal 95% CI for the OR, were presented from the final adjusted model.

> Reviewer Comment: Conclusions regarding this VE analysis have some limitations, since the results are based on analyses performed *post hoc* (i.e., hypotheses not pre-specified) and based on data from an observational retrospective (i.e., non-randomized, prone to more missing or inconsistent data compared to prospective study design) study. Sensitivity analyses were performed to assess for possible effects of excluding non-third trimester exposures, missing data, and ambiguous or multiple Tdap exposures on the VE estimate.

Primary Objective: Bayesian analysis
The informative prior was derived from a Bayesian meta-analysis of four epidemiological studies, which provided a range of plausible values for Boostrix-specific VE estimates to prevent pertussis in infants 2 to 3 months of age when Boostrix (US or non-US formulation) was administered to mothers during pregnancy. For additional information about the systematic literature review used for selecting the studies, please see section 5.5.2 of this memo. One of the studies, Amirthalingam et al. (2016), was replaced by an unpublished report from PHE (Andrews et al. 2020) that uses the same analysis methods as Amirthalingam et al. (2016) but comprises a longer study period. The VE estimates used in the prior were 87.3% (34.2%, 97.5%) (Bellido-Blasco et al 2017), 64% (18%, 84%) (Saul et al. 2018), 89% (72%, 96%) (Uriarte et al. 2019), 87% (84%, 90%).

For the Bayesian analysis, the predictive prior was a weighted (i.e., robustified) combination of an informative prior (Bayesian meta-analytic prior), and an uninformative, vague prior.

Sensitivity analyses included an assessment of the impact of the weights on the VE and 95% credible interval estimates, which took into consideration the weights for the informative prior ranging between 0% and 100%.

Please see CBER statistical review memo for additional details about frequentist analysis methods, Bayesian meta-analysis framework, and other sensitivity analyses.

Changes to the Planned Analyses
The Applicant's re-analysis included data from infants <2 weeks of age. Infants in the control group were also matched by age (<2 weeks old, ≥2 weeks old) within each stratum defined by birth hospital.

The CDC provided corrections to several mothers' exposure timing classifications, based on additional information gathered after the Skoff et al. 2017 publication:

- 2 participants should have been classified as vaccinated before pregnancy
- 1 participant should have been classified as vaccinated after pregnancy

The Applicant incorporated these corrections into a revised dataset provided in sBLA amendment 10, and this corrected dataset was used for all results in this review.

6.1.4 Study Population

6.1.4.1 Subject Disposition

EPI-PERTUSSIS-052 dataset included all infants born to mothers who were classified as unexposed or as exposed to Boostrix during or after pregnancy and whose matching stratum included at least one case and one control. Main reason for exclusion from EPI-PERTUSSIS-052 re-analysis dataset was that the mother received a Tdap vaccine other than Boostrix.

Table 2. Subject Disposition, Study EPI-PERTUSSIS-052

Population	Cases n (%)	Matched Controls n (%)
Infants from CDC study	251 (100)	682 (100)
EPI-PERTUSSIS-052 re-analysis set	108 (43.0)	183 (26.8)

Source: Created from Skoff et al. 2017 and EPI-PERTUSSIS-052 (BLA 125106/1469.10) and Skoff (MF5-27946/0.3) datasets
n/%=number/percentage of participants in a given category

6.1.4.2 Demographic and Baseline Characteristics

Table 3 shows the demographics of the infant cases and matched controls. Similar to the CDC study population (Skoff et al. 2017), a higher percentage of EPI-PERTUSSIS-052 cases were Hispanic, born to a mother with less education, and lived in a larger household (3 or more people), and had a household member diagnosed with pertussis recently, compared to the control group.

Table 3. Demographic and Baseline Characteristics, Infants 0 to 8 Weeks of Age, by Case Status, Study EPI-PERTUSSIS-052

Demographic or Baseline Characteristics	Cases n (%)	Controls n (%)
Total Number of Participants[a]	109	186
Infant's Age (Weeks)	---	---
0 to <2	4 (3.7)	6 (3.2)
2 to <3	30 (27.5)	56 (30.1)
4 to <5	28 (25.7)	54 (29.0)
6 to <7	36 (33.0)	7 (3.8)
7 to ≤ 8	11 (10.1)	19 (10.2)
Infant's Sex	---	---
Male	59 (54.1)	92 (49.5)
Female	50 (45.9)	94 (50.5)
Infant's Race	---	---
White	89 (81.7)	144 (77.4)
Black	9 (8.3)	13 (7.0)
Other	10 (9.2)	22 (11.8)
Missing	1 (0.9)	7 (3.8)
Infant's Ethnicity	---	---
Hispanic	69 (63.3)	108 (58.1)
Not Hispanic	39 (35.8)	78 (41.9)
Missing	1 (0.9)	0
Infant's State of Birth	---	---
California	77 (70.6)	130 (69.9)
Connecticut	7 (6.4)	13 (7.0)
Minnesota	7 (6.4)	11 (5.9)
New Mexico	10 (9.2)	19 (10.2)

Demographic or Baseline Characteristics	Cases n (%)	Controls n (%)
New York	5 (4.6)	7 (3.8)
Oregon	3 (2.8)	6 (3.2)
Infant's Pertussis Vaccination[b]	---	---
Known Exposure	2 (1.8)	0
No Known Exposure	107 (98.2)	184 (98.9)
Unknown Exposure Type	0	2 (1.1)
Mother's Education Status	---	---
High school or less	72 (66.1)	67 (36.0)
More than high school	37 (33.9)	119 (64.0)
Family Size	---	---
Two or fewer	6 (5.5)	49 (26.3)
Three or more	103 (94.5)	137 (73.7)
Pertussis Diagnosis at Home	---	---
Yes	6 (5.5)	0
No	103 (94.5)	185 (100)

Source: Created from the EPI-PERTUSSIS-052 (BLA 125106/1469.10) and Skoff (MF5-27946/0.3) datasets
N=total number of participants. n/%=number/percentage of participants in a given category
Age (weeks)=age expressed in weeks at the date of the onset of cough
a. Includes 1 case that was excluded by GSK because of missing ethnicity and the associated 3 matched controls (because their matching case was missing ethnicity). Please see sensitivity analysis #3 results, based on this analysis set, in section 6.1.5.2.2 of this memo.
b. Infants exposed to a pertussis-containing vaccine at least 14 days before their index date.

6.1.4.3 Maternal Boostrix Exposure

Table 4 presents the timing of vaccination for mothers exposed to Boostrix, and mothers unexposed to Boostrix (unvaccinated). 4 cases and 18 controls were born to mothers who received Boostrix during the third trimester of pregnancy.

Table 4. Timing of Maternal Exposure to Boostrix, Study EPI-PERTUSSIS-052

Maternal Vaccination Timing	Cases N=109[a] (%)	Controls N=186[a] (%)
Unvaccinated	76 (69.7)	116 (62.4)
Before pregnancy	1 (0.9)	5 (2.7)
First or second trimester	1 (0.9)	6 (3.2)
Third trimester	4 (3.7)	18 (9.7)
After pregnancy	27 (24.8)	41 (22.0)

Source: Created from the EPI-PERTUSSIS-052 (BLA 125106/1469.10) and Skoff (MF5-27946/0.3) datasets
a. Includes 1 case that was excluded by GSK because of missing ethnicity and the associated 3 matched controls (because their matching case was missing ethnicity). Please see sensitivity analysis #3 results, based on this analysis set, in section 6.1.5.2.2 of this memo.

Vaccine brand or manufacturer unknown or inconsistent

Among vaccine exposed mothers in the CDC study, approximately 11% of cases and controls were born to mothers vaccinated with a Tdap vaccine for which the manufacturer and brand were unknown, and for 4 mothers (2 case, 2 control), only the manufacturer (GSK) or brand (Boostrix) was documented. There was 1 control for which the Tdap vaccine administered to the mother was recorded inconsistently (vaccine brand recorded as Boostrix and manufacturer recorded as Sanofi). Please see CBER statistical review memo for further details.

Multiple exposures to Tdap vaccine

Five mothers were vaccinated with a Tdap within 1 year or less, with Boostrix as the most recent vaccine administered (before pregnancy n=1, after pregnancy n=3, third trimester n=1).

Another mother received Boostrix during the third trimester and a Tdap vaccine (unknown vaccine manufacturer and brand) after pregnancy. Please see CBER statistical review memo for further details.

6.1.5 Effectiveness Analyses Results

6.1.5.1 Primary Objective: Frequentist Re-analysis of Pertussis Cases

The analysis set for the frequentist analysis of pertussis cases included 108 cases and 183 controls, of which 4 cases and 18 controls were exposed to Boostrix in the third trimester. VE when Boostrix was administered in the third trimester of pregnancy was estimated from a conditional logistic regression model adjusted for infant age, maternal education, and household size, resulting in a VE estimate of 78.0% (95% CI: -38.0, 96.5).

Sensitivity analyses accounting for the effects of excluding non-third trimester exposures, missing data, and ambiguous or multiple Tdap vaccine exposures in mothers were generally consistent with the primary analysis results (see Table 5. Bayesian Sensitivity Analysis Results, below). Please see section 6.1.5.2.2.

6.1.5.2 Primary Objective: Bayesian Re-analysis

6.1.5.2.1 Bayesian Meta-Analytic Prior (MAP)

The MAP distribution of VE curves upward around 50%, indicating that VEs > 50% are highly likely, and peaks around 80%, indicating that VEs around 80% are most likely, which is consistent with the results of the individual studies used to derive the prior. The weighted (robustified) MAP distribution is flatter, indicating that Boostrix VEs > 50% are only slightly more likely than VEs < 50%. This defines a conservative prior for VE for the Bayesian analysis.

6.1.5.2.2 Bayesian Re-analysis Results

The VE of Boostrix to prevent pertussis in infants <2 months of age when Boostrix was administered to mothers in the third trimester of pregnancy was estimated using informative prior weights ranging from 10% to 90%. The informative prior was constructed from studies that provided estimates of Boostrix-specific VE to prevent pertussis in infants approximately 2 months of age whose mothers were vaccinated during pregnancy.

When the informative prior had 20% weight, the VE was 81.5% (95% credible interval: 12.9, 94.5). When the informative prior had 90% weight, the VE was 83.4% (95% credible interval: 55.7, 92.5). The estimated VE was consistent, regardless of the weight applied to the informative prior, and 95% credible interval lower bound was >0% for informative prior weights of 20% and greater.

Sensitivity analyses accounting for the relative weight given to the informative prior and the studies included in the informative prior produced similar results.

Table 5. Bayesian Sensitivity Analysis Results, Study EPI-PERTUSSIS-052

Sensitivity Analysis	VE (%)	95% CI LL	95% CI UL
1	87.2	39.5	96.0
2	79.7	81.4	90.5
3	83.3	54.5	92.4
4	73.7	22.5	88.1

Source: Amendment 12. page 2, Table 1.
Mixing weight = weight given to the informative historical predictive prior. The complementary weight is given to the vague prior.
VE = vaccine effectiveness based on a meta-analytic-predictive prior from historical control considering a 90% mixing weight.
LL = lower limit of 95% credible interval (CI). UL = upper limit of 95% credible interval (CI)

In sensitivity analysis #1, exclusion of infants whose mothers were vaccinated pre/post pregnancy and in 1st/2nd trimester resulted in wider 95% credibility intervals (from LL 55,7, UL 92.5 to LL 39.5, UL 96.0).

In sensitivity analysis #2, the VE estimate was numerically lower since a control infant whose mother was not vaccinated was removed from the re-analysis and 2 mothers of cases initially classified as vaccinated after pregnancy were reclassified as vaccinated during the 3rd trimester.

The VE from sensitivity analysis #3, which included 1 case/control with an unknown ethnicity, was similar to the VE estimate of the Bayesian re-analysis.

In sensitivity analysis #4, the VE estimate was numerically lower, possibly due to inclusion of mothers of cases and/or controls who were vaccinated with Td vaccine (i.e., unvaccinated against pertussis) instead of Tdap.

6.1.5.3 Subpopulation Analyses

Subgroup analyses based on race, sex, and ethnicity of the infant cases and controls were not provided. Overall, the study population was mainly White (79%) and Hispanic (60%); the remaining number of case and control participants are too small to conduct meaningful analyses.

6.1.6 Study Summary and Conclusions

EPI-PERTUSSIS-052 was the main study to support the effectiveness of Boostrix immunization of pregnant individuals during the third trimester to prevent pertussis in infants <2 months of age. In this study, Boostrix-relevant data were re-analyzed from an observational case-control study of Tdap VE (Skoff et al. 2017) within a Bayesian meta-analysis framework. The use of real world evidence was considered an acceptable regulatory approach to confirming VE since conduct of a randomized, placebo-controlled, Boostrix (US formulation) study in pregnant individuals was not feasible due to an existing CDC recommendation for use during each pregnancy.

Since many infants in the case control study were born to mothers vaccinated with another Tdap vaccine (Adacel) and the resultant numbers of infant cases and controls born to mothers vaccinated with Boostrix during the third trimester was small (108 cases, including 4 cases whose mothers received Boostrix during the third trimester; 183 controls, including 18 whose mothers received Boostrix during the third trimester). Adjusting for infant age, maternal education, and household size, the effectiveness of Boostrix maternal vaccination when administered to mothers during third trimester of pregnancy was 78.0% (95% CI: -38.0, 96.5). While the point estimate was consistent with the vaccine non-brand specific analysis in Skoff et al., effectiveness of Boostrix maternal immunization was not confirmed by this study alone, as

signified by the wide confidence interval and negative lower 95% confidence limit for VE. Additional analyses were performed to characterize Boostrix effectiveness within a Bayesian meta-analysis framework.

A systematic literature review was performed by the Applicant, and four Boostrix observational studies were used to define the prior for the Bayesian reanalysis of the Skoff et al. data. The observational studies provided a range of plausible values for VE, given the current scientific understanding of vaccination during pregnancy, to prevent pertussis in infants <2-3 months of age whose mothers were immunized with Boostrix (US or non-US formulation) during pregnancy. The studies were similar but not identical in their population, design, and analysis to the case-control study that generates the data used to calculate the posterior. Including a wider range of plausible values in the prior, even if from less similar studies, makes the prior more vague and increases the strength of evidence needed from the data to demonstrate effectiveness.

For the Bayesian meta-analysis, the predictive prior was a weighted (i.e., robustified) combination of an informative prior (Bayesian meta-analytic prior), and an uninformative, vague prior. When the informative prior had 20% weight, the Bayesian update resulted in a VE of 81.5% (95% credible interval: 12.9, 94.5). When the informative prior had 90% weight, the Bayesian update resulted in a VE of 83.4% (95% credible interval: 55.7, 92.5). The VE point estimates were consistent, regardless of the weight applied to the informative prior, which additionally supported Boostrix effectiveness in preventing pertussis in infants less than 2 months old when administered to their mothers during the third trimester of pregnancy. In conclusion, given the prior and the EPI-PERTUSSIS-052 data, there is a 95% probability that the true VE falls within the 95% credible interval. That is, while the point estimate is the most likely VE, the credible interval gives the range of VEs that are highly likely, given the prior and the data from study EPI-PERTUSSIS-052.

Interpretations of EPI-PERTUSSIS-052 re-analyses have some limitations. The re-analyses were performed *post hoc* (e.g., hypotheses not pre-specified). Second, the re-analyses were based on a dataset from a retrospective observational study; the participants were not randomized, and there could be more missing or inconsistent data compared to a prospective study design. The sensitivity analyses based on the study EPI-PERTUSSIS-052 dataset were preformed to assess for effects of excluding non-third trimester exposures, missing data, and ambiguous or multiple Tdap vaccine exposures in mothers; the results of these analyses and the Bayesian sensitivity analysis results were generally consistent with the primary analysis results. Third, in the Skoff et al. case-control study, infant cases and controls were matched by birth hospital and age, which might not have accounted for other confounding factors, such as household size and maternal education. The re-analyses in EPI-PERTUSSIS-052 took into account household size, and maternal education; the VE point estimate was consistent with the vaccine non-brand specific analysis in the case control study.

6.2 Study DTPA-BOOSTRIX-047

NCT# 02377349
Title: A phase 4, observer-blind, randomized, cross-over, placebo-controlled, multicenter study to assess the immunogenicity and safety of a single dose of Boostrix in pregnant women.

The study design and data presented in this section pertain to pregnancy and fetal/neonatal outcomes when Boostrix was administered to pregnant individuals during the 3rd trimester. Other study objectives (e.g., assessment of transplacental pertussis, tetanus and diphtheria

antibodies, safety of Boostrix administered within 72 hours post-delivery, vaccination of household contacts) were not presented in this memo, since these objectives were not relevant to the safety of Boostrix for the proposed indication.

6.2.1 Objectives

Safety Objectives and Endpoints

1. To assess the safety of Boostrix in pregnant women, administered during $27^{0/7}$-$36^{6/7}$ weeks of gestation, in terms of pregnancy outcomes, pregnancy-related and neonate-related adverse events (AEs) of interest.

   Endpoints:
   - Pregnancy outcomes:
     - live birth, stillbirth, or elective termination with no congenital anomalies
     - live birth with congenital anomalies
     - stillbirth with congenital anomalies
     - elective termination with congenital anomalies

   - Pregnancy/neonatal-related AEs of interest occurring up to the end of study follow up (2 months post-delivery): gestational diabetes, pregnancy-related hypertension, premature rupture of membranes, preterm premature rupture of membranes, premature labor, premature uterine contractions, intrauterine growth restriction/poor fetal growth, pre-eclampsia, eclampsia, vaginal or intrauterine hemorrhage, maternal death, preterm birth, neonatal death, small for gestational age, neonatal hypoxic ischemic encephalopathy and failure to thrive/growth deficiency.

2. To evaluate the safety of Boostrix administered to individuals during pregnancy and post-delivery in terms of
   a. Solicited AEs during the 8 days (Day 0-7) after vaccination
   b. Unsolicited AEs during the 31-days (Days 0-30) after vaccination
   c. Serious adverse events (SAEs) during the period from Visit 1 (Day 0) up to Visit 4 (post-delivery Month 2)

Reviewer Comment: In this study, conducted outside the US, participants received the non-US formulation of Boostrix, which contains the same aP, D and T, antigens and in the same quantities as Boostrix. The non-US formulation contains more aluminum/per dose than Boostrix (0.5 mg vs. 0.3 mg).

6.2.2 Design Overview

This study was designed as an observer-blind, randomized, placebo-controlled study. A total of 680 pregnant women 18-45 years of age were randomized (1:1) to the following study groups:

Table 6. Study DTPA-047 Design

Study Group	3rd Trimester of Pregnancy[a]	Post-delivery[b]
Tdap	Boostrix[c]	Placebo (saline)
Control	Placebo (saline)	Boostrix[c]

a. $27^{0/7}$-$36^{6/7}$ weeks of gestation
b. within 72 hours after delivery
c. non-US Boostrix formulation

Observer-blind: the vaccine recipient and study personnel collecting the safety information, but not the vaccine administrator, were blinded to the treatment assignment.

Study site, age of the pregnant participant (18- <25 years, 25- <35 years and 35- <46 years), gestational age of fetus (27-32 weeks and 33-36 weeks), and country were minimization factors for randomization.

6.2.3 Population

Inclusion criteria

- Healthy pregnant women 18-45 years of age inclusive at the time of screening. Pregnancy: $27^{0/7}$-$36^{6/7}$ weeks of gestation (by ultrasound examination) at Visit 1.
- Not at high risk for complications, as determined by the obstetrical algorithm for identification of eligible participants and the Obstetrical Risk Assessment Form.
- No significant fetal abnormalities, as observed by the level II ultrasound testing conducted after 18 weeks of gestation.
- Nuchal translucency scan, serum testing and any other prenatal tests, if conducted, suggesting normal pregnancy.
- Willing to have the infant born immunized with Infanrix hexa and Prevnar 13, as per national recommendations, in the follow-up clinical studies DTPA-048 PRI and DTPA-049 BST.
- Did not plan to give the child for adoption.
- Able to comply with protocol procedures.
- Written informed consent was obtained.

Exclusion criteria

- Previous vaccination containing diphtheria, tetanus or pertussis antigens or diphtheria and tetanus toxoids at any time during the current pregnancy.
- Serious underlying medical condition (e.g., immunosuppressive disease or therapy, human immunodeficiency virus infection, collagen vascular disease, epilepsy, diabetes mellitus, chronic hypertension, moderate to severe asthma, lung/heart disease, liver/kidney disease, infections including TORCH [toxoplasmosis, rubella, cytomegalovirus, herpes simplex, syphilis] infections).
- Co-morbid medical or obstetric conditions that in the opinion of the investigator had the potential to complicate the pregnancy course and outcomes, e.g., hypertension (requiring medications), uterine anomalies, bleeding disorders.
- Gestational diabetes as determined by glucose tolerance test conducted after 20 weeks of gestation, as per local recommendations of the country.
- History of early onset (<34 weeks of gestation) of eclampsia/pre-eclampsia in previous pregnancy.
- Diagnosed with multiple pregnancies (twins, triplets etc.).
- History of major congenital anomalies in previous pregnancies.
- Family history (first-degree relatives only) of congenital anomalies, recurrent pregnancy losses (2 or more consecutive losses) and unexplained neonatal death(s) in the subject.
- History of physician-diagnosed or laboratory-confirmed pertussis within the past 5 years.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.
- Any medical condition that in the judgment of the investigator would make intramuscular injection unsafe.

- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 6 months prior to the first vaccine. For corticosteroids, this meant prednisone ≥20 mg/day, or equivalent. Inhaled and topical steroids were allowed.
- Administration of immunoglobulins and/or any blood products within the 3 months preceding the dose of study vaccine, or planned administration during the study period, with the exception of anti-D (Rh)-immunoglobulin.
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine anytime during the current pregnancy or planned use during the study period.
- Planned administration/administration of a vaccine within 30 days before and 30 days after the dose of study vaccine. Exception: seasonal influenza vaccine can be administered at any time during the study.
- Concurrently participating in another clinical study, at any time during the study, in which the subject had been or was to be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).
- History of febrile illness within the past 72 hours. Fever was defined as temperature ≥37.5°C for oral, axillary or tympanic route.
- Acute disease and/or fever at the time of enrollment. Participants with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may be enrolled at the discretion of the investigator.

6.2.4 Study Treatments or Agents Mandated by the Protocol

- Boostrix (non-US formulation): each 0.5 mL contained 5 Lf tetanus toxoid, 2.5 Lf diphtheria toxoid, 8 mcg inactivated PT, 8 mcg FHA, 2.5 mcg PRN, and 0.5 mg aluminum adjuvant. Supplied in pre-filled syringes.

- Placebo (saline). Supplied in pre-filled syringes.

6.2.5 Directions for Use

A single dose (0.5 mL) of non-US Boostrix or placebo was administered intramuscularly.

6.2.6 Sites and Centers

The study was conducted at a total of 27 sites in Australia (3), Canada (4), Czechia (5), Finland (5), Italy (5) and Spain (12).

6.2.7 Surveillance/Monitoring

- Solicited adverse events (Day 0-7; Day 0: day of vaccination)
  Local: pain, redness, swelling at the injection site. Grading scale:
  - Redness, swelling: grade 1 (Mild) <20 mm, grade 2 (moderate) 20-<50 mm, grade 3 (severe) >50 mm.
  - Pain: Mild: pain present but does not interfere with daily activities. Moderate: painful when limb is moved and interferes with daily activities. Severe: significant pain at rest, prevents daily activities.

  Systemic: fatigue, headache, nausea, vomiting, diarrhea, abdominal pain, fever.
  Grade 1 (mild) = easily tolerated by the subject, causes minimal discomfort and does not interfere with daily activities.
  Grade 2 (moderate) = interferes with daily activities.
  Grade 3 (severe) = prevents daily activities, e.g., unable to go to work.

Fever: T ≥37.5°C oral, axillary or tympanic route. The preferred route for temperature measurement is oral/axillary. Reported in 0.5°C increments.

- Unsolicited AEs (Days 0-30)
- SAEs: from Day 0 through post-delivery Month 2 (Tdap group). In the control group, SAEs were assessed from the day of placebo dose during pregnancy, then 2 months after non-US Boostrix dose administered post-partum (within 72 hrs of delivery).

- Pregnancy outcomes (Day 0 to post-delivery Month 2)
  - Live birth
  - Spontaneous pregnancy loss, including spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation), ectopic and molar pregnancy, stillbirth (defined as intrauterine death of fetus after 22 weeks of gestation, based on the EMA Guideline on pregnancy exposure (EMA 2006)).
  - Early neonatal death (i.e., death of a live born infant occurring within the first 7 days of life).
  - Any congenital anomaly or birth defect (as defined in CDC 2021b) identified in the offspring of a study patient (either during pregnancy, at birth or later) regardless of whether the fetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

- Pregnancy/neonatal-related AEs of interest: gestational diabetes, pregnancy-related hypertension, premature rupture of membranes, preterm premature rupture of membranes, premature labor, premature uterine contractions, intrauterine growth restriction/poor fetal growth, pre-eclampsia, eclampsia, vaginal or intrauterine hemorrhage, maternal death, preterm birth, neonatal death, small for gestational age, neonatal hypoxic ischemic encephalopathy and failure to thrive/growth deficiency.

An Independent Data Monitoring Committee (IDMC) periodically reviewed unblinded safety data. The IDMC was comprised of an obstetrician, a pediatrician, a statistician and a neuro-developmental specialist. The Safety Review Team (SRT) was responsible for reviewing the blinded safety data on a regular basis to identify any potential safety issues or signals to evaluate and agree on action plans, if necessary. The SRT included a Central Safety Physician, Safety Scientist, Clinical Research and Development Lead, Biostatistician, and Epidemiology and Regulatory representatives.

6.2.8 Statistical Considerations & Statistical Analysis Plan

The precision achieved with 300 participants in each group for pregnancy outcomes pregnancy-related adverse events of interest/neonate-related events of interest in terms of 95% CIs.

Table 7. Precision in Each Group for Pre-specified Pregnancy Outcomes and Pregnancy-Related Adverse Events of Interest/ Neonate-Related Events of Interest

Outcome	n (%)	95%CI LL	95% CI UL
Stillbirth	1 (0.3)	0.0	1.8
Placental Abruption	3 (1.0)	0.2	2.9
Placenta previa	1 (0.3)	0.0	1.8
Post-partum hemorrhage	18 (6.0)	3.6	9.3
Premature rupture of membranes	24 (8.0)	5.2	11.7
Premature uterine contractions and premature labor	36 (12.0)	8.5	16.2
Preterm delivery	35 (11.7)	8.3	15.7
Intrauterine growth restriction	30 (10.0)	6.8	14.0
Pregnancy related hypertension, preeclampsia and eclampsia	36 (12.0)	8.5	16.2
Gestational diabetes	15 (5.0)	2.8	8.1
Congenital anomalies (major anomalies)	9 (3.0)	1.4	5.6

Source: 125106.1469 047-protcol.pdf, page 86, Table 17.
N= 300 participants in the total vaccinated cohort, n = number of participants with any pregnancy outcome. % = (n/N); LL = Lower limit; UL = Upper limit.

Safety analyses

- Percentages of participants reporting a pre-specified pregnancy outcome, pregnancy-related adverse event of interest/neonate-related events of interest, with 95% CIs.
- Incidence of local reactions and systemic events within 7 days after each vaccination, categorized by adverse event, severity and vaccine group, with 95% CIs. Occurrence of fever was reported in 0.5°C increments.
- Occurrence of unsolicited AEs, classified by MedDRA preferred terms
- Description of SAEs reported from Day 0 to 2 months after delivery.

6.2.9 Study Population and Disposition

The first subject was enrolled in the study on October 14, 2015, and the last study visit was on October 24, 2017.

6.2.9.1 Populations Analyzed

Total Vaccinated Cohort: all participants with documented study vaccination. Analyses were performed according to the study product administered. Safety analyses were based on the TVC.

6.2.9.1.1 Demographics

The median age in the vaccine and placebo group was 33 years. Overall, 93.0% of vaccine recipients and 94.2% placebo recipients were White.

Table 8. Demographics and Baseline Characteristics[a], Study DTPA-047

Characteristic	Tdap N=341 Value or n (%)	Control N=346 Value or n (%)
Age (Years)		
18 to 24	10 (2.9)	13 (3.8)
25 to 34	214 (62.8)	215 (62.1)
35 to 45	117 (34.3)	118 (34.1)
Mean	32.7	32.5
Median	33.0	33.0
Race		
African Heritage/African American	3 (0.9)	9 (2.6)
American Indian or Alaskan Native	2 (0.6)	0 (0)
Asian	9 (2.7)	2 (0.6)
White	317 (93.0)	326 (94.2)
Other	10 (2.9)	9 (2.6)
Gestational week at vaccination		
<27	0 (0)	1* (0.3)
27 to 32	204 (59.8)	200 (57.8)
33 to 36	136 (39.9)	145 (41.9)
>36	1 (0.3)	0 (0)
Gestational week at delivery		
Mean	39.1	39.3
Median	39	39

Source: 116945-047.pdf, page 89, adapted from Table 20.
Total Vaccinated Cohort
In this table, Tdap group=Mothers received Boostrix (non-US formulation) during pregnancy, control group=Mothers received placebo during pregnancy.
N=number of participants, n=number of participants in a given category, Value=value of the considered parameter. %=n/Number of participants with available results.
*This subject was considered in the 'below 27 weeks of gestation at dose 1' for analysis, however after database freeze it was confirmed by the investigator that the gestational age for this subject was 27 weeks at dose 1.

6.2.9.1.2 Subject Disposition

The Total Vaccinated Cohort (TVC) consisted of 687 participants (341 Tdap, 346 control).

Table 9. Number of Participants Vaccinated, Who Completed Visit 4 and Reason for Not Attending Visit 4, Study DTPA-047, Total Vaccinated Cohort

Disposition	Tdap	Control	Total
Vaccinated	341	346	687
Completed last study visit	325	335	660

Source: 116945-047.pdf, page 86, Table 17.
In this table, Tdap group=mothers received Boostrix (non-US formulation) during pregnancy, control group=mothers received placebo during pregnancy.

6.2.10 Safety Results

6.2.10.1 Solicited Adverse Events

During Days 0-7 after pregnant women in the Tdap group received non-US Boostrix and the control group received placebo (Table 10):

- Solicited local AEs: Injection site pain was the most frequently reported solicited local AE, reported for 86.3% of participants in Tdap group and 14.6% of participants in the control

group. Grade 3 injection site pain (defined as significant pain at rest, prevented daily activities) was reported for 2.1% of participants in the Tdap group and none in the control group.

- Solicited general AEs: Fatigue was the most frequently reported solicited general AE, reported for 43.6% and 36.3% of participants in the Tdap group and control group, respectively. Fatigue was also the most frequently reported Grade 3 solicited general AE, reported for 1.8% and 1.5% of participants in the Tdap group and control group, respectively.

Table 10. Frequency of Solicited Local AEs Within 8 Days After 1 Dose in Pregnant Women[a], Study DTPA-047

AE	Tdap N=335 n (%)	Control N=343 n (%)
Pain	--	--
Any	289 (86.3)	50 (14.6)
Grade 3	7 (2.1)	0
Redness (mm)	--	--
Any	96 (28.7)	44 (12.8)
>20	23 (6.9)	1 (0.3)
>50	3 (0.9)	0
Swelling (mm)	--	--
Any	84 (25.1)	12 (3.5)
>20	23 (6.9)	1 (0.3)
>50	3 (0.9)	0

Source: DTPA-047 report, page 104, adapted from Table 32.
a. Total vaccinated cohort
In this table, Tdap group=mothers received Boostrix (non-US formulation) during pregnancy, control group=mothers received placebo during pregnancy.

The frequency of solicited local AEs within 8 days after the post-partum dose is shown in Table 11.

Table 11. Frequency of Solicited Local AEs Within 8 Days After 1 Dose Administered Post-partum[a], Study DTPA-047

AE	Tdap N=324 n (%)	Control N=330 n (%)
Pain	--	--
Any	41 (12.7)	207 (62.7)
Grade 3	2 (0.6)	14 (4.2)
Redness (mm)	--	--
Any	34 (10.5)	98 (29.7)
>20	2 (0.6)	16 (4.8)
>50	0	3 (0.9)
Swelling (mm)	--	--
Any	17 (5.2)	87 (26.4)
>20	0	16 (4.8)
>50	0	4 (1.2)

Source: DTPA-047 report, page 104, adapted from Table 33.
a. Total vaccinated cohort
In this table, the Tdap group received placebo (saline) and control received non-US Boostrix post-partum (within 72 hours after delivery).

6.2.10.2 Unsolicited AEs (Days 0-30) after pregnancy dose

Overall, 38.7% and 35.5% of participants in the Tdap group and control group, respectively, reported at least one unsolicited AE. Except for adverse reactions consistent with solicited local and general AEs, none of the AEs in the Tdap group after the pregnancy dose were considered by the study investigator to be at least possibly related to vaccination. This clinical reviewer agrees with the investigators' assessments.

6.2.10.3 Deaths

No deaths were reported during the course of the study.

6.2.10.4 Nonfatal Serious Adverse Events

During the time period from the vaccine dose administered during pregnancy to post-delivery Month 2:

- A total of 56 SAEs were reported for 45 participants (13.2%) in the Tdap group and a total of 64 SAEs were reported for 48 participants (13.9%) in the control group. Premature rupture of membranes was the most frequently reported SAE, reported in 3.8% and 4.3% of participants in Tdap group and control group, respectively.

- 1 participant in the control group was hospitalized for premature labor at 36 weeks gestation, which was 18 days after placebo (saline) was administered. The study investigator considered the event to be at least possibly related to study intervention because, although premature labor may be related to factors intrinsic to the mother or fetus, the possibility of external influence, such as third trimester vaccination, could not be fully ruled out. The Applicant considered the event to be related more to premature rupture of membranes than to the study intervention. Also the event rate among the control group was within the expected event rate in the general population. This reviewer agrees with the Applicant's assessment.

6.2.10.5 Pregnancy Outcomes

Table 12. Percentage of Participants by Pregnancy Outcome, Study DTPA-047, Total Vaccinated Cohort[a]

Category	Tdap[b] N=341 n (%)	Control[b] N=346 n (%)
Live infant no apparent congenital anomaly	332 (97.4)	337 (97.4)
Live infant with congenital anomaly	9 (2.6)	8 (2.3)
Lost to follow-up	0 (0.0)	1 (0.3)

Source: 116945-047.pdf, page 119, Table 44.

a. N=number of participants with at least 1 administered dose. n (%) = number (percentage) of participants reporting a specific pregnancy outcome.

b. The Tdap group received Boostrix in the third trimester pregnancy and placebo (saline) post-partum (with 72 hours after delivery). The control group received placebo (saline) in the third trimester pregnancy and Boostrix post-partum (with 72 hours after delivery).

No participants reported stillbirth or elective termination.

6.2.10.6 Pregnancy-Related and Fetal/Neonatal Adverse Events of Special Interest

Table 13. Percentage of Participants with Listed Pregnancy/Neonate-Related Adverse Events of Interest, Total Vaccinated Cohort[a], Study DTPA-047

Category	Tdap[b] N=341 n (%)	Control[b] N=346 n %
Intrauterine growth restriction/poor fetal growth	5 (1.5)	2 (0.6)
Pre-eclampsia	1 (0.3)	5 (1.4)
Pregnancy-related hypertension	4 (1.2)	5 (1.4)
Premature labor	13 (3.8)	11 (3.2)
Premature rupture of membranes	13 (3.8)	15 (4.3)
Premature uterine contractions	2 (0.6)	3 (0.9)
Preterm birth	11 (3.2)	9 (2.6)
Preterm premature rupture of membranes	4 (1.2)	7 (2.0)
Small for gestational age	2 (0.6)	2 (0.6)
Vaginal or intrauterine hemorrhage	9 (2.6)	10 (2.9)

Source: 116945-047.pdf, page 118, Table 43.

a. N=number of participants with at least 1 administered dose. n (%)=number (percentage) of participants in a given category.

b. The Tdap group received Boostrix in the third trimester pregnancy and placebo (saline) post-partum (with 72 hours after delivery). The control group received placebo (saline) in the third trimester pregnancy and Boostrix post-partum (with 72 hours after delivery).

No participants reported gestational diabetes, eclampsia, neonatal death, neonatal hypoxic, ischemic encephalopathy or failure to thrive/growth deficiency.

6.2.10.7 Dropouts and/or Discontinuations

A single participant in the Tdap group withdrew from the study at due to an SAE (respiratory distress) at birth, reported for an infant born to a vaccinated mother. The event occurred 66 days after the mother received Boostrix in the third trimester. The infant was born at 40 4/7 weeks gestation by vaginal delivery, with bruising to the occiput; birth weight was 7lbs 13 oz. APGAR scores were 3, 7, and 9. The study investigator considered the SAE to be caused by vaccination of the mother during pregnancy. This clinical reviewer considers the event to be unrelated to study intervention due to other plausible reasons (occipital bruising, large for gestational age) for respiratory distress.

6.2.11 Study Summary and Conclusions

Study DTPA-047 was designed as an observer-blind, randomized, controlled trial in pregnant women 18-45 years of age. A total of 690 women received non-US formulation of Boostrix (n=341) or saline placebo (n=346) during the third trimester of pregnancy. Post-partum (within 72 hours of delivery), the Tdap group received saline placebo and the control group received the non-US formulation of Boostrix. The safety data with the non-US formulation are relevant because the non-US formulation of Boostrix contains the same antigens and in the same quantities as Boostrix, but contains more aluminum (as aluminum hydroxide adjuvant) per dose.

There were no identified vaccine-related adverse effects on pregnancy or the fetus/newborn child from Day 0 (vaccination during the third trimester) to 2 months post-delivery. The rates of reported solicited adverse reactions following receipt of the non-US formulation of Boostrix administered during pregnancy were consistent with the rates following receipt of the non-US formulation of Boostrix administered to study participants postpartum. Rates of solicited AEs observed in this study are likely higher that rates expected with the US-licensed formulation due less aluminum hydroxide adjuvant in the US formulation.

6.3 Studies DTPA-Boostrix-048 PRI and DTPA-Boostrix-049 BST

NCT# 02422264 study DTPA-Boostrix-048 PRI

Title: "A phase IV, open-label, non-randomized study to assess the immunogenicity and safety of *Infanrix hexa* administered as primary vaccination in healthy infants born to mothers given *Boostrix* during pregnancy or post-delivery in study 116945 [DTPA (BOOSTRIX)-047]"

NCT# 02853929 study DTPA-Boostrix-049 BST

Title: "A phase 4, phase IV, open-label, non-randomized study to assess the immunogenicity and safety of a booster dose of *Infanrix hexa* in healthy infants born to study DTPA BOOSTRIX-047 mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery"

The purpose of these studies were to evaluate if the presence of transplacentally transferred maternal antibodies could potentially interfere with pertussis antibody responses in infants following a DTaP-HBV-IPV-Hib primary vaccination series and after a booster dose.

Design

The safety and immunogenicity of a non-US licensed DTaP-HBV-IPV-Hib vaccine (Infanrix Hexa) was assessed after a primary series (study DTPA-Boostrix-048 PRI) and after a booster dose (study DTPA-Boostrix-049 BST) in infants born to former study DTPA-Boostrix-047 maternal participants who received Boostrix (Tdap group) or saline placebo (control group) during pregnancy. Prevnar 13 (PCV13; Wyeth Pharmaceuticals) was co-administered with DTaP-HBV-IPV-Hib, per local country recommendations. Both studies were designed as open-label, non-randomized, multicenter studies.

> ***Reviewer Comment***:
> The safety and immunogenicity data with the non-US licensed DTaP-HBV-IPV-Hib vaccine are relevant because the vaccine contains the same antigens and in the same quantities as other US-licensed DTaP-containing vaccines.
>
> Since participants completing the DTaP-HBV-IPV-Hib primary series and booster dose were older than the intended population (i.e., infants < 2 months of age) for the proposed indication, only SAEs are described in this memo.

A 2- or 3- dose DTaP-HBV-IPV-Hib primary series was administered to infants starting at 6-14 weeks of age, followed by a DTaP-HBV-IPV-Hib booster dose administered at 11 to 19 months of age; the schedule of administered vaccines was in accordance with local country recommendations.

The safety of DTaP-HBV-IPV-Hib was assessed by occurrences of solicited reactions and unsolicited AEs, including SAEs. SAEs were monitored from Day 0 to 30 days after the last DTaP-HBV-IPV-Hib primary series dose, and from the day of the DTaP-HBV-IPV-Hib booster dose to 30 days after the booster dose.

A blood sample was collected 30 days after the primary series dose and 21-48 days after the booster dose. Sera were tested at GSK laboratories (Clinical Laboratory Sciences) in Belgium.

Results

Safety (30 days after the last DTaP-HBV-IPV-Hib primary dose and after the booster dose)

Among infants born to mothers who received Boostrix during the third trimester of pregnancy, at least 1 SAE was reported after the last DTaP-HBV-IPV-Hib primary dose in 7 of the infants (2.4%; congenital CMV, ear malformation, bronchiolitis, UTI, fracture, altered state of consciousness), compared with 17 (5.6%) infants born to mothers who received saline placebo during the third trimester of pregnancy.

Among infants born to mothers who received Boostrix, no SAEs were reported after the DTaP-HBV-IPV-Hib booster dose. No deaths were reported during the course of the study.

Immunogenicity
The results presented in this section are antibody responses to pertussis vaccine antigens evaluated in participants who received a 3-dose DTaP-HBV-IPV-Hib primary series administered at 2,4 and 6 months of age and a DTaP-HBV-IPV-Hib booster dose at 12-18 months of age, which is the schedule that is consistent with the ACIP recommendations for childhood immunizations.

Overall, 528 infants who received a 3-dose DTaP-HBV-IPV-Hib primary series, of which 457 received DTaP-HBV-IPV-Hib at 2, 4, and 6 months of age (enrolled at sites in Australia, Canada, and Spain), and 416 infants received a DTaP-HBV-IPV-Hib booster dose as toddlers. For the primary series, the according to protocol (ATP) population included a total of 400 participants (203 infants born to mothers who received Boostrix during pregnancy, 197 infants born to mothers who received placebo during pregnancy). For the booster dose, the ATP population included a total of 363 (177 infants born to mothers who received Boostrix during pregnancy, 186 infants born to mothers who received placebo during pregnancy) .

At 1 month after the last DTaP-HBV-IPV-Hib primary dose, the pertussis PT, FHA, and PRN geometric mean concentrations (GMCs) were 33, 73, and 67, respectively, in infants born to mothers who received Boostrix during the third trimester of pregnancy, and 57,113, and 102, respectively, in infants born to mothers who received saline placebo during the third trimester of pregnancy.

At 1 month after the booster dose, the PT, FHA, and PRN GMCs were 52,167, and 379, respectively, in infants born to mothers who received Boostrix during the third trimester of pregnancy, and 77, 178, and 262, respectively, in infants born to mothers who received saline placebo during the third trimester of pregnancy.

Summary and Conclusions

No safety concerns were identified among infants born to mothers who received Boostrix during the third trimester of pregnancy.

Data are not available on immune responses to US licensed vaccines administered on the US schedule among infants born to mothers who received Boostrix during pregnancy.

In infants whose mothers received Boostrix (non-US formulation) during the third trimester of pregnancy, antibody responses to a non-US licensed DTaP-containing vaccine were diminished anti-PT, anti-FHA and anti-PRN following the primary series, and for anti-PT and anti-FHA

following a booster dose compared to infants who received the same vaccine but whose mothers received placebo during pregnancy. Whether the diminished immune responses observed in vaccinated infants whose mothers received Boostrix (non-US formulation) during pregnancy result in diminished effectiveness of pertussis vaccination in infants is unknown.

7. INTEGRATED OVERVIEW OF EFFICACY

No integrated summary of efficacy is presented in this memo, since effectiveness for the proposed indication was based on the single study EPI-PERTUSSIS 052 VE US DB. Immunogenicity data from infants in studies DTPA-Boostrix-048 and DTPA-Boostrix 049 discussed are separately (see section 6.3).

8. INTEGRATED OVERVIEW OF SAFETY

No integrated summary of safety is presented in this memo, since study DTPA-Boostrix-047 was the only study that described pregnancy and neonatal outcomes.

9. ADDITIONAL CLINICAL ISSUES

9.1 Specific Populations

9.1.1 Human Pregnancy Data

Please see clinical review of study DTPA-Boostrix-047 (section 6.2 of this memo).

9.1.2 Use During Lactation

No data are available to assess the effect of administration of Boostrix on breastfed infants or on milk production/excretion.

9.1.3 Pediatric Use and PREA Considerations

This supplement triggers PREA because a new indication is being requested for the product.

- A partial waiver for studies in pregnant individuals <10 years of age was granted because the vaccine does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group.

- The pediatric study requirement for pregnant individuals 10 through 16 years of age was fulfilled via extrapolation of safety and effectiveness of Boostrix in pregnant individuals 18 to 45 years of age because the course of pertussis disease in the offspring, immune responses to vaccination, and transplacental transfer of pertussis maternal antibodies, is expected to be similar in pregnant adolescents as compared to pregnant adults. Boostrix is approved for active booster immunization in individuals 10 years of age and older to prevent pertussis, tetanus, and diphtheria.

9.1.4 Immunocompromised Patients

No data available

10. CONCLUSIONS

The safety and effectiveness data in this sBLA support revisions to the Boostrix prescribing information for the proposed indication and use.

11. Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Considerations

Table 14. Risk-Benefit Assessment

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Pertussis disease, caused by the bacterium *Bordetella pertussis*, is a respiratory illness affecting all age groups. The morbidity associated with pertussis is highest in infants <6 months of age; in 2021, the highest incidence of reported pertussis cases in the US was in infants <6 months of age. The case-fatality rate for pertussis among infants younger than six months of age was approximately 1%, with the majority of deaths occurring in those younger than two months of age. The most common complications of pertussis infection in infants include apnea, pneumonia, and weight loss secondary to feeding difficulties and post-tussive vomiting. Other complications include seizures and encephalopathy.	Pertussis in infants is a serious medical condition, and can be associated with severe complications and long-term sequelae.
Unmet Medical Need	Management of infant pertussis infection includes antimicrobial therapy and supportive care. Preventive measures include age-appropriate immunization against pertussis for infants starting as early as 6 weeks of age, children, adolescents, adults, and unimmunized/partially immunized close contacts of the index case.	Primary active immunization of infants against pertussis consists of a multiple dose series, beginning as early as 6 weeks of age. There is an unmet medical need for effective prevention in infants, especially in infants younger than 2 months of age.
Clinical Benefit	• The effectiveness of Boostrix immunization during the third trimester of pregnancy to prevent pertussis among infants <2 months of age was based on a re-analysis of Boostrix data (study EPI-PERTUSSIS-052) from an observational case-control study of Tdap vaccine effectiveness (VE) within a Bayesian meta-analysis framework. The preliminary VE estimate was 78.0% (95% CI: -38.0, 96.5) for Boostrix vaccination during the third trimester of pregnancy. • The EPI-PERTUSSIS-052 re-analyses were performed *post hoc* and based on data from a retrospective observational study (Skoff et al. 2017).	• Immunization during pregnancy can provide passive protection against pertussis in infants younger than 2 months of age. • Overall, results of the re-analyses of Boostrix data from the case-control study (Skoff et al. 2017) within a Bayesian meta-analysis framework demonstrated that Boostrix was statistically likely to be effective for the intended indication, and the results were robust to the analysis methods and missing data.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The safety of non-US formulation Boostrix (0.5 mg aluminum/per dose) administered to women during the third trimester of pregnancy was evaluated in study DTPA-Boostrix-047, a randomized, controlled clinical trial. No vaccine-related adverse effect on pregnancy or the fetus/newborn child were identified. • The rates of reported solicited adverse reactions following receipt of the non-US formulation of Boostrix administered during pregnancy were consistent with the rates following receipt of the non-US formulation of Boostrix administered to study participants postpartum. • The safety data with the non-US formulation are relevant because the non-US formulation of Boostrix contains the same antigens and in the same quantities as Boostrix.	The clinical and observational data provided in the license application supplement support the safety of Boostrix when administered during the third trimester of pregnancy for both vaccinated mothers and infants.
Risk Management	• Since CDC's recommendation in 2012, there has been widespread use of Tdap vaccines during pregnancy. Review of pregnancy registry data (EPI-PERTUSSIS 028) suggested there was no risk to the mother, the fetus, or the infant from routine vaccination in the third trimester of pregnancy. Interpretation of potential risks associated with vaccination during pregnancy in this registry was limited because observational data were mainly reported retrospectively and 93% of pregnancy registry participants were lost to follow-up.	• The Applicant proposes to conduct a Boostrix Pregnancy registry study as a post-approval commitment. Study EPI-PERTUSSIS-075 VS US PR will be designed as an observational, exposure cohort study to evaluate pregnancy outcomes in individuals exposed to Boostrix during the third trimester of pregnancy.

11.2 Risk-Benefit Summary and Assessment

The benefit of Boostrix immunization during the third trimester of pregnancy to prevent pertussis in infants <2 months of age was supported by results from a re-analysis of Boostrix data (study EPI-PERTUSSIS-052) within a Bayesian meta-analysis framework. Prevention of pertussis in infants younger than 2 months of age could potentially prevent severe complications and long-term sequelae associate with pertussis disease.

Following receipt of the non-US formulation of Boostrix administered during pregnancy, the known and potential risks include common local and systemic adverse reactions (e.g., pain/redness/swelling at the injection site, fatigue). No vaccine-related adverse effect on pregnancy or the fetus/newborn child were identified.

In infants whose mothers received Boostrix (non-US formulation) during the third trimester of pregnancy, antibody responses to a non-US licensed DTaP-containing vaccine were diminished for certain pertussis vaccine antigens following a primary series and booster dose, compared to infants who received the same vaccine but whose mothers received placebo during pregnancy.

In conclusion, pertussis in infants is a serious, and sometimes fatal, medical condition that can lead to severe complications and long-term sequelae, especially in infants younger than 2 months of age. The benefit of Boostrix administered to individuals during the third trimester of pregnancy to prevent pertussis in infants younger than 2 months of age outweighs the potential risks and uncertainties about decrease effectiveness due to diminished pertussis antibody responses in these infants following primary vaccination series and after a booster dose with DTaP-containing vaccines.

11.4 Recommendations on Regulatory Actions

Based on review of the safety and effectiveness data in this sBLA and the risk-benefit considerations described in section 11, I recommend approval of Boostrix for immunization during the third trimester of pregnancy to prevent pertussis in infants younger than 2 months of age.

11.5 Labeling Review and Recommendations

The prescribing information was reviewed and specific comments on the labeling were provided by CBER to the Applicant who made the requested revisions. All issues were satisfactorily resolved.

11.6 Recommendations on Postmarketing Action

The Applicant committed to conduct a post-marketing registry-based study, Study EPI-PERTUSSIS-075 VS US PR, an observational, exposure cohort study, to evaluate pregnancy outcomes in individuals exposed to Boostrix as of the 1st day of the 27th week of gestation compared to pregnancy outcomes in individuals who do not receive any Tdap vaccine during pregnancy. The registry study will continue for at least 4 years.

Study EPI-PERTUSSIS-075 VS US PR
- Final Protocol Submission: January 31, 2023
- Study Completion: December 31, 2026
- Final Study Report Submission: January 31, 2027

APPENDIX A. DEFINITIONS AND EVALUATIONS OF SELECTED TERMS AND ADVERSE EVENTS OF INTEREST, STUDY DTPA-047

Pregnancy-related terms

- Gestational age: Dating from:
  - 1st day of last menstrual period (LMP), or
  - 1st trimester ultrasound if no known LMP or the ultrasound is not consistent with LMP, or
  - known date of fertilization (e.g., by Assisted Reproductive Technology or Intrauterine Insemination)
- Trimester of gestation
  - 1st trimester: up to and including 13 6/7 weeks of gestation
  - 2nd trimester: 14 0/7 weeks to 27 6/7 weeks of gestation
  - 3rd trimester: 28 0/7 weeks of gestation and beyond
- Length of pregnancy
  - Preterm: up to and including 36 6/7 weeks of gestation
  - Term: 37 0/7 weeks through 41 6/7 weeks of gestation
  - Early term: Birth at 37 0/7 to <39 weeks of gestation
  - Post-term: 42 0/7 weeks of gestation and beyond

Pregnancy outcomes

- Live birth: Delivery of a live infant, regardless of maturity or birth weight, as determined by the presence of spontaneous respirations, a heartbeat, and spontaneous movement.

- Spontaneous abortion
  - Pregnancy ending spontaneously before 22 weeks of gestation (i.e., up to and including 21 6/7 weeks of gestation). Includes death of embryo/ fetus *in utero* (missed abortion), or blighted ovum /anembryonic pregnancy (i.e., fertilized ovum whose development has ceased at an early stage).

  Subgroups: Early miscarriage: occurs during the 1st trimester. Late miscarriage: occurs during the 2nd trimester.

- Stillbirth: Delivery of dead fetus after 22 0/7 weeks of gestation; during pregnancy or antepartum, intrapartum.

  Subgroups: Early Stillbirth: Delivery 22 0/7 – <28 weeks and/or ≥500 -1000 grams. Late Stillbirth: Delivery ≥28 0/7 weeks and/or >1,000 grams.

- Congenital anomalies (as defined in CDC 2021b), including morphological, functional, chromosomal or genetic anomalies, regardless of whether detected at birth or not, the fetus is delivered dead or alive, or defects are identified by prenatal ultrasound, amniocentesis or examination of the products of conception. Live-born neonates with transient (postural) defects, infectious conditions or certain biochemical disorders are classified as being without congenital anomalies unless there is a reasonable possibility that the condition reflects an unrecognized congenital birth defect.

  Morphological anomalies: Abnormalities of body structure or function that are present at birth and are of prenatal origin.
  - Minor anomaly: Anatomic variant or defect that do not have serious medical, functional or cosmetic consequences for the child. Includes those found in association with major anomalies.

- Major anomaly: Structural or functional defect that require surgical/medical treatment, have serious adverse effects on health or development (functional), or have significant cosmetic impact.

- Elective or therapeutic termination of pregnancy: Expulsion of products of conception with medical or surgical assistance.
  - Elective: performed for personal choice/socioeconomic reasons, excluding maternal or fetal health reasons.
  - Therapeutic: performed to preserve the health or save the life of a pregnant woman.

- Ectopic pregnancy: Condition in which a fertilized ovum implants outside the uterine cavity, most often in the fallopian tube (97%).

- Molar pregnancy: Pregnancy marked by a neoplasm within the uterus, whereby part or all of the chorionic villi are converted into a mass of clear vesicles. Histologically distinct disease entities encompassed by this general terminology include: complete and partial hydatidiform moles, invasive moles, gestational choriocarcinomas, and placental site trophoblastic tumors.

<u>Pregnancy-related adverse events of interest</u>

- Vaginal or intrauterine hemorrhage: Vaginal or intrauterine hemorrhage that encompasses antepartum (i.e. bleeding from the genital tract after 24 weeks of gestation), intrapartum, and postpartum bleeding (i.e. within 24 hours postdelivery). A major obstetric hemorrhage is defined as blood loss from uterus or genital tract >1500 mL or a decrease in hemoglobin of >4 gr/dl or acute loss requiring transfusion of >4 units of blood, or signs or symptoms of hypovolemia.

- Premature rupture of membranes (PROM) and preterm premature rupture of membranes (P-PROM)
  - PROM: Spontaneous rupture of fetal membranes that occurs before the onset of labor.
  - Preterm PROM (P-PROM): Spontaneous rupture of fetal membranes that occurs before the onset of labor before 37 weeks gestation.

- Premature uterine contractions and premature labor
  - Premature uterine contractions: Uterine contractions without cervical change.
  - Premature labor: Cervical change in the presence of regular uterine contractions that occur before 37 weeks of gestation.

- Intrauterine growth restriction / poor fetal growth: Estimated or actual birth weight below the 10^{th} percentile for gestational age.

- Gestational hypertension, preeclampsia, and eclampsia
  - Gestational hypertension: Blood pressure systolic >140 and/or diastolic >90 mmHg, documented in at least 2 separate measurements after 20 weeks of gestation, without proteinuria or other stigmata of preeclampsia, and returning to normal postpartum. Hypertension usually resolves by 12 weeks postpartum.
  - Pre-eclampsia: Hypertension (>140 and/or >90 mmHg) occurring after the 20th week of gestation, and up to 6 weeks postpartum, combined with other abnormalities such as proteinuria (>300 mg in a 24 hr urine specimen).

- HELLP syndrome: Form of severe pre-eclampsia with associated laboratory abnormalities including hemolysis (H), elevated liver (EL) function tests, and low platelets (LP), with or without proteinuria.
- Eclampsia: If the features of preeclampsia are accompanied by new onset generalized seizures.
- Chronic hypertension with superimposed preeclampsia: Chronic hypertension definition plus preeclampsia definition.

- Gestational diabetes mellitus: Onset or first recognition of abnormal glucose tolerance during pregnancy. Diagnosis based on administration of glucose challenge test at 24-28 weeks gestation.

- Maternal death: Death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes.
  - Direct obstetric death: death of the mother resulting from conditions or complications which are unique to pregnancy and occur during the antepartum, intrapartum, or postpartum period.
  - Indirect obstetric death: A maternal death that is not directly due to obstetric cause (such as from previously existing disease, or disease developing during pregnancy, labor, or the puerperium but that was not unique to pregnancy).
  - Late maternal death: Death of woman from direct or indirect causes more than 42 days but less than one year after termination of pregnancy.

<u>Neonatal-related events of interest</u>

- Birth weight
  - Small for gestational age: Birth weight <10% for newborns of same gestational age and gender in same population (<2500 g at term).
    - Low birth weight: BW <2500 g (5.5 lb).
    - Very low birth weight : BW <1500 g (3.3 lb).
    - Extremely low birth weight: BW <1000 g (2.2 lb)
  - Large for gestational age: Birth weight >90% for newborns of same gestational age in same population (>4000g at term).
    - High Birth Weight (Macrosomia): BW >4000 g (8.1 lb).

- Preterm birth: Birth before 37 weeks of gestation.
  - Late preterm: 34 to <37 weeks
  - Moderate preterm: 32 to <34 weeks
  - Very preterm: 28 to <32 weeks
  - Extreme preterm: <28 weeks

- Neonatal death: Death of newborn at any time from birth to 28 days of life, regardless of gestational age.

  Subgroups:
  - Very early neonatal death: <24hrs
  - Early neonatal death: from birth to <7 days
  - Late neonatal death: 7 to <28 days

- Intrapartum-related neonatal death (previously called: asphyxia deaths): neonatal death of term babies with neonatal encephalopathy or who cannot be resuscitated (or for whom resuscitation is not available). Also includes babies who die from birth injury without hypoxic brain injury)

- Neonatal hypoxic ischemic encephalopathy: A disturbance of neurological function in the earliest days of life in the term infant manifested by difficulty initiation and maintaining respiration, depression of tone and reflexes, abnormal level of consciousness and often seizures, which may follow an intrapartum hypoxic insult or be due to another cause.

- Failure to thrive or growth deficiency: Inability to maintain expected growth rate over time, evaluated by plotting individual weight gain and growth on standard growth charts for the population.